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Annals of Surgery

A Monthly Review of
Surgical Science and Practice
since 1885

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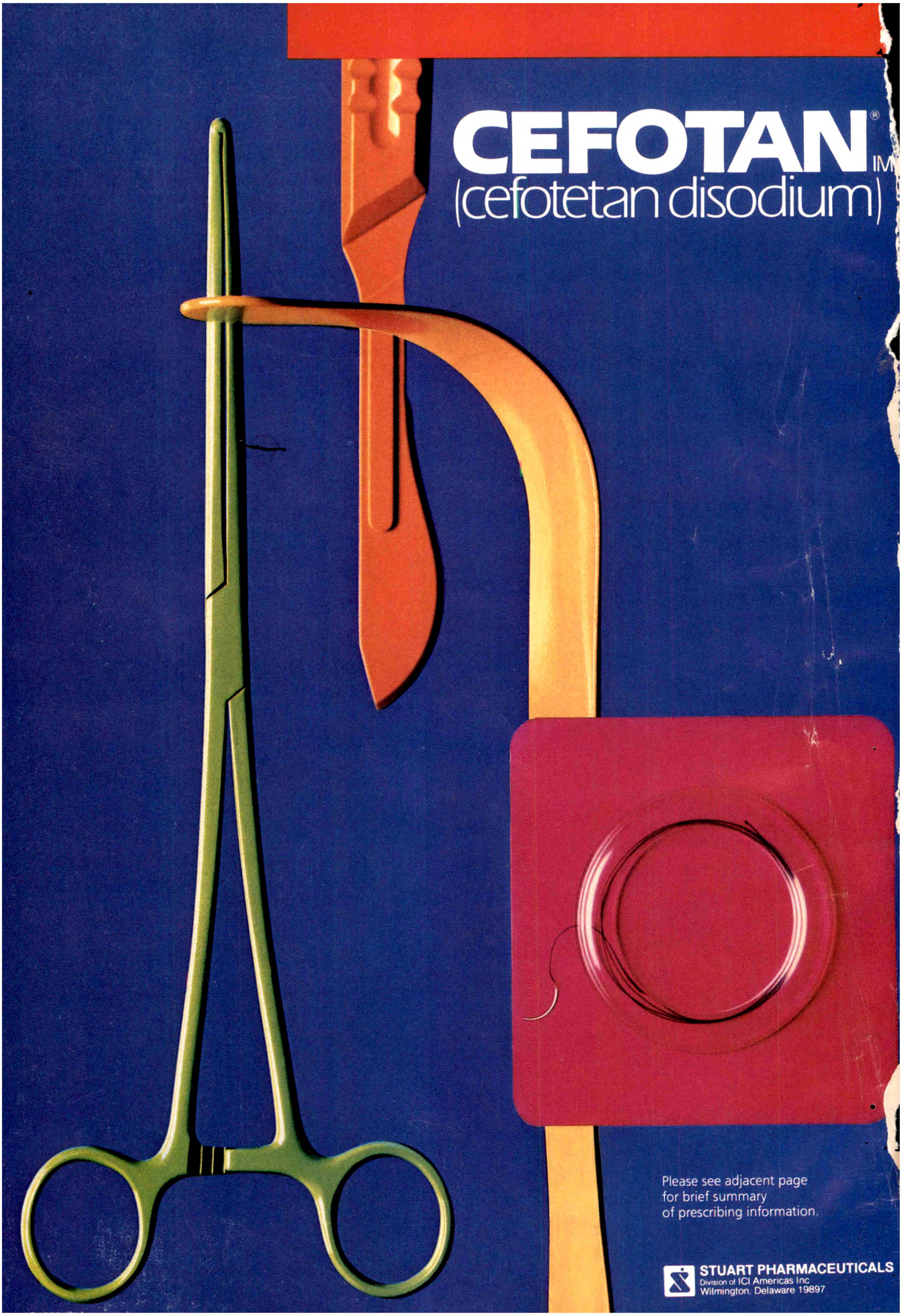

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BRIEF SUMMARY

INDICATIONS AND USAGE
TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary tract infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris*, *Providencia rettgeri*, and *Morganella morganii*).

Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.

Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.

Gynecologic infections caused by *Staphylococcus aureus*† (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus* species (excluding enterococci), *E coli*, *Proteus mirabilis*, *Neisseria gonorrhoeae*, *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*), *Fusobacterium* species,† and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species†).

Intra-abdominal infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*†), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*).

Bone and joint infections caused by *Staphylococcus aureus*.†

***NOTE:** Some strains of *Staphylococcus epidermidis* are resistant to cefotetan.

†Efficacy for this organism in this organ system was studied in fewer than ten infections.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS
CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS
Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.

PRECAUTIONS
GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state. Prothrombin times should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, [illegible]) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels of Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

* Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approx 8-16 times the usual adult human dose) on days 6-35 of life (thought to be

developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approx 2-4 times the usual human dose), only 1 of 10 treated animals was affected, and the degree of degeneration was mild. Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
In clinical studies the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5 percent of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4 percent of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2 percent of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2 percent of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than one percent of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

DOSAGE AND ADMINISTRATION
TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dose*	Every 12 hours
10-30	Usual Recommended Dose*	Every 24 hours
<10	Usual Recommended Dose*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED
CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.
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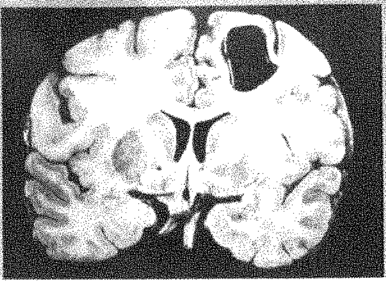
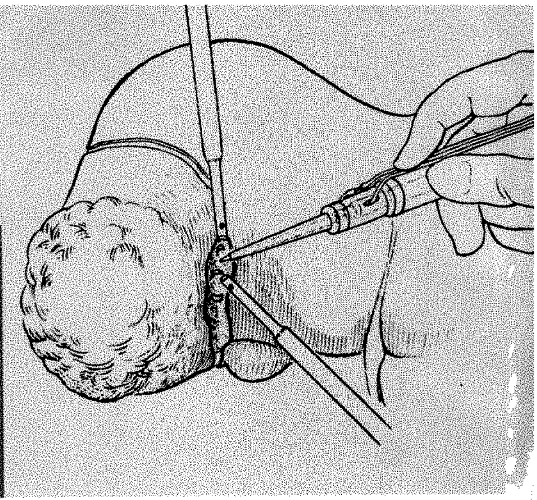




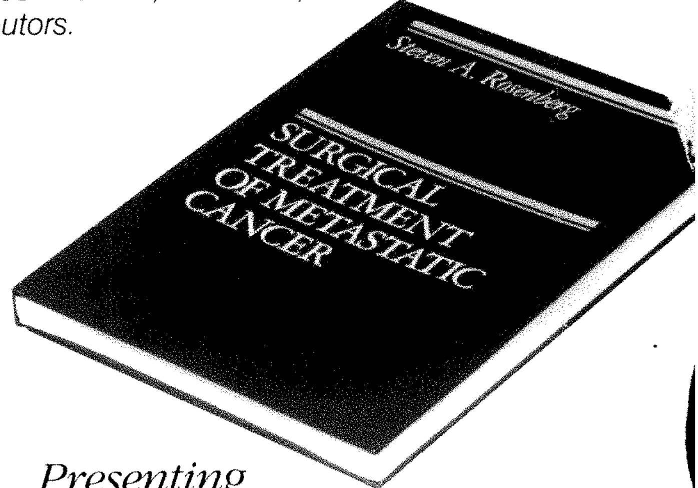
SURGICAL TREATMENT of METASTATIC CANCER

Edited by Steven A. Rosenberg, M.D., Ph.D.

Chief of Surgery, National Cancer Institute, Bethesda, MD.

9 contributors.

> *❝ For many patients with isolated visceral metastases from solid tumors, surgical resection of those metastatic deposits represents the best opportunity for cure. For patients with solitary pulmonary and hepatic metastases, up to 30% of patients may experience prolonged disease-free survival after metastasectomy. Only a small subset of patients with metastatic cancer are likely to benefit from surgical resection and identification of these patients is an important part of the application of this treatment. ❞*
>
> **—from the *Preface***



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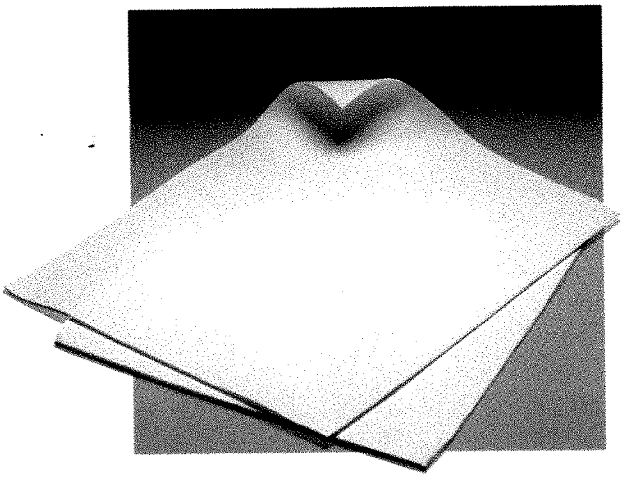

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INDICATIONS AND USAGE: Thrombostat (Thrombin, USP) is indicated as an aid in hemostasis wherever oozing blood from capillaries and small venules is accessible.

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CONTRAINDICATIONS: Thrombostat is contraindicated in persons known to be sensitive to any of its components and/or to material of bovine origin.

WARNING: Because of its action in the clotting mechanism, Thrombostat must not be injected or otherwise allowed to enter large blood vessels. Extensive intravascular clotting and even death may result. Thrombostat is an antigenic substance and has caused sensitivity and allergic reactions when injected into animals.

PRECAUTIONS: General: Consult the absorbable gelatin sponge product labeling for complete information for use prior to utilizing the thrombin-saturated-sponge procedure.

Pregnancy—Teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with Thrombin, Topical (Bovine). It is also not known whether Thrombin, Topical (Bovine) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Thrombin, Topical (Bovine) should be given to a pregnant woman only if clearly indicated.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: An allergic type reaction following the use of Thrombostat for treatment of epistaxis has been reported. Febrile reactions have also been observed following the use of Thrombostat in certain surgical procedures but no cause-effect relationship has been established.

DOSAGE AND ADMINISTRATION: General: Solutions of Thrombostat may be prepared in sterile distilled water or isotonic saline. The intended use determines the strength of the solution to prepare. For general use in plastic surgery, dental extractions, skin grafting, neurosurgery, etc, solutions containing approximately 100 units per ml are frequently used. For this, 10 ml of diluent added to the 1000 unit package is suitable. Where bleeding is profuse, as from cut surfaces of liver and spleen, concentrations as high as 1000 to 2000 units per ml may be required. For this the 5000 unit vial dissolved in 5 ml or 2.5 ml respectively, of the diluent supplied in the package is convenient. Intermediate strengths to suit the needs of the case may be prepared by selecting the proper strength package and dissolving the contents in an appropriate volume of diluent. In many situations, it may be advantageous to use Thrombostat (Thrombin, USP) in dry form on oozing surfaces.

Caution: Solutions should be used the day they are prepared. The solution may be used for up to 6 hours when stored at room temperature; up to 24 hours when stored under refrigeration, and, if necessary, up to 48 hours when stored frozen.

The following techniques are suggested for the topical application of Thrombostat.

1. The recipient surface should be sponged (not wiped) free of blood before Thrombostat is applied.
2. A spray may be used or the surface may be flooded using a sterile syringe and small gauge needle. The most effective hemostasis results when the Thrombostat mixes freely with the blood as soon as it reaches the surface.
3. In instances where Thrombostat in dry form is needed, the vial is opened by removing the metal ring by flipping up the plastic cap and tearing counterclockwise. The rubber-diaphragm cap may be easily removed and the dried Thrombostat is then broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.
4. Sponging of treated surfaces should be avoided in order that the clot remain securely in place.

Thrombostat may be used in conjunction with Absorbable Gelatin Sponge, USP as follows:

1. Prepare Thrombostat solution of the desired strength.
2. Immerse sponge strips of the desired size in the Thrombostat solution. Knead the sponge strips vigorously with moistened gloved fingers to remove trapped air, thereby facilitating saturation of the sponge.
3. Apply saturated sponge to bleeding area. Hold in place for 10 to 15 seconds with a pledget of cotton or a small gauze sponge.

Thrombostat Kit: Thrombostat Kit contains one sterile 20,000 unit vial of Thrombostat, one sterile vial of Isotonic Saline Diluent, and one sterile pump sprayer cap. The Kit may be used as follows:

1. Remove the Tyvek blister lid by pulling up at the indicated corner. The sterile inner tray can be lifted out or introduced into the operating field.
2. The cover to the sterile inner tray is removed by pulling up on the finger tab, exposing the sterile contents.
3. Thrombostat solution of the desired strength is prepared and the pump sprayer cap inserted and seated on the Thrombostat solution vial. Note: Several strokes of the pump sprayer will be required before the Thrombostat solution is expelled.
4. Alternatively, when Thrombostat in dry form is needed, the vial is opened as described above and the dried Thrombostat broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.

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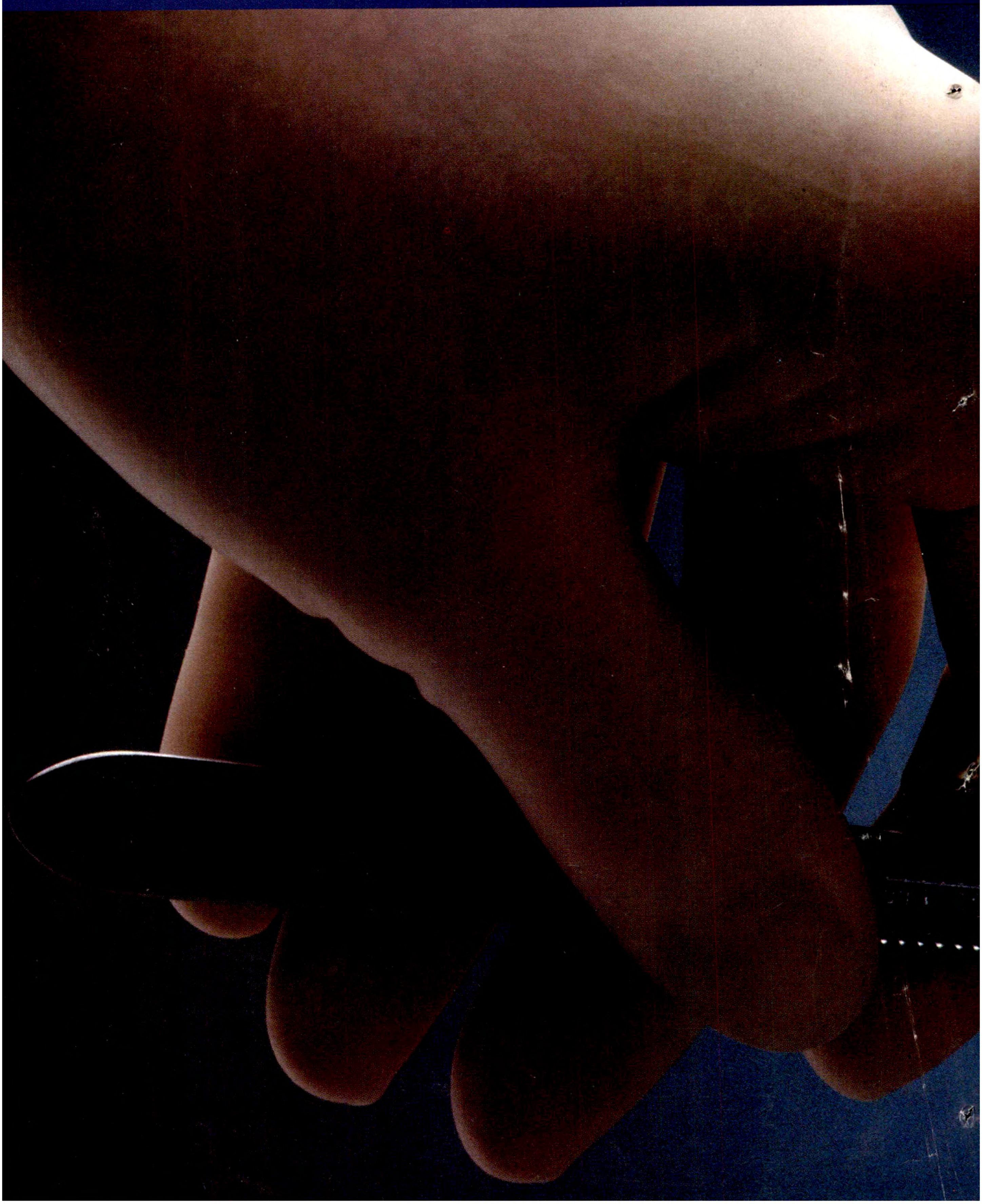

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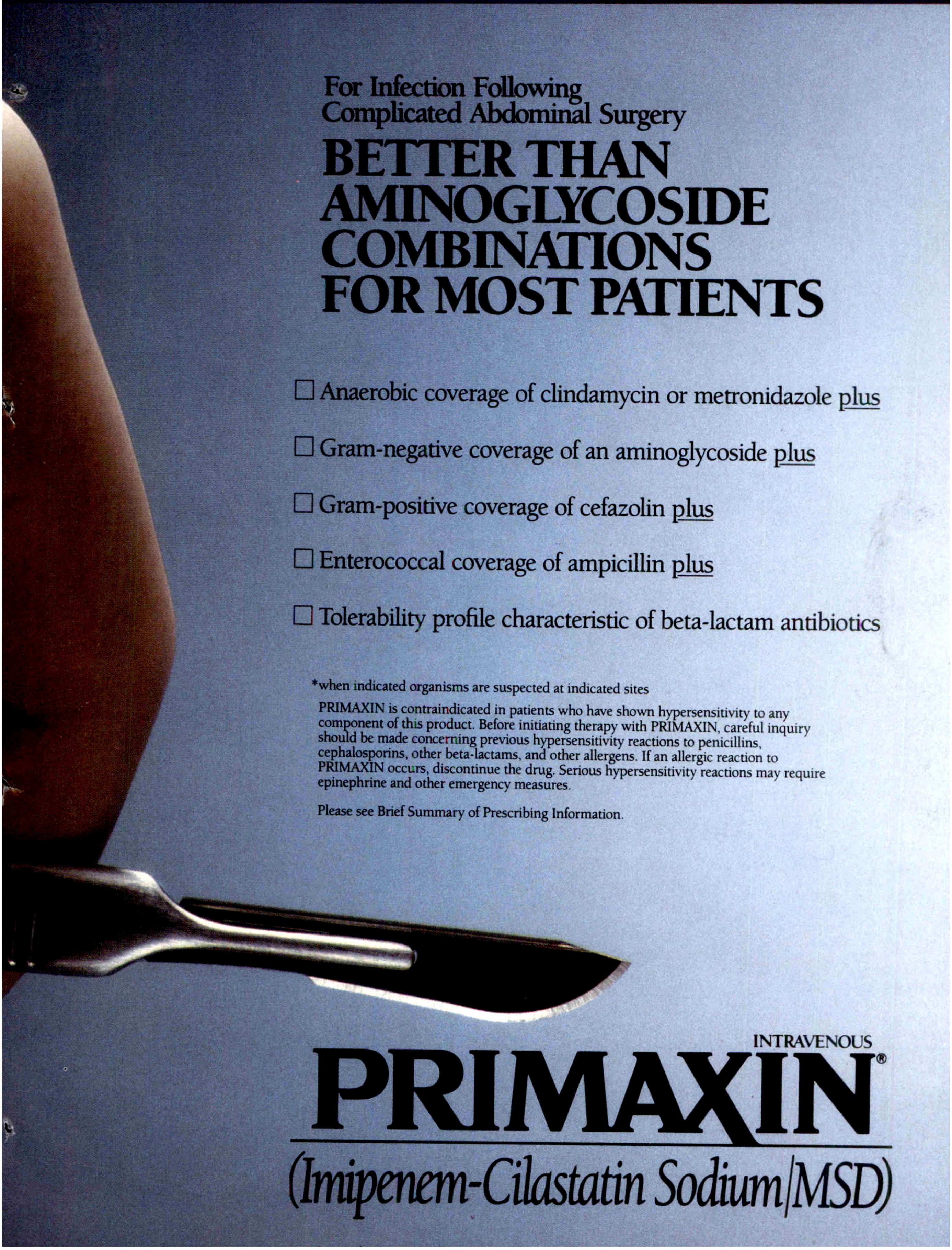

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PRIMAXIN is contraindicated in patients who have shown hypersensitivity to any component of this product. Before initiating therapy with PRIMAXIN, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams, and other allergens. If an allergic reaction to PRIMAXIN occurs, discontinue the drug. Serious hypersensitivity reactions may require epinephrine and other emergency measures.

Please see Brief Summary of Prescribing Information.

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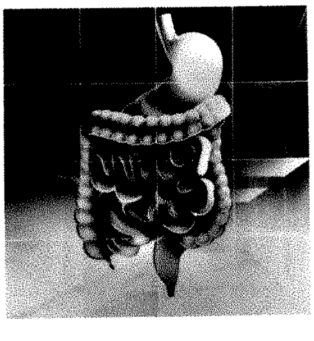

Contraindications: PRIMAXIN is contraindicated in patients who have shown hypersensitivity to any component of this product.

Warnings: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH BETA LACTAMS. THESE REACTIONS ARE MORE APT TO OCCUR IN PERSONS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER BETA LACTAM. BEFORE INITIATING THERAPY WITH 'PRIMAXIN', CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA LACTAMS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION TO 'PRIMAXIN' OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with virtually all antibiotics, including PRIMAXIN; therefore it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. This colitis may range in severity from mild to life threatening.

Mild cases of pseudomembranous colitis may respond to drug discontinuance alone. In more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte, and protein supplementation, and the use of a drug such as oral vancomycin, as indicated. Isolation of the patient may be advisable. Other causes of colitis should also be considered.

Precautions: *General*—CNS adverse experiences such as confusional states, myoclonic activity, and seizures have been reported during treatment with PRIMAXIN, especially when recommended dosages were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. However, there have been reports of CNS adverse experiences in patients who had no recognized or documented underlying CNS disorder or compromised renal function.

Patients with severe or marked impairment of renal function, whether or not undergoing hemodialysis, had a higher risk of seizure activity when receiving maximum recommended doses than those with no impairment of renal function; therefore, maximum recommended doses should be used only where clearly indicated (see DOSAGE AND ADMINISTRATION).

Patients with creatinine clearances of ≤ 5 mL/min/1.73 m^2 should not receive PRIMAXIN unless hemodialysis is instituted within 48 hours.

For patients on hemodialysis, PRIMAXIN is recommended only when the benefit outweighs the potential risk of seizures.

Close adherence to the recommended dosage and dosage schedules is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of PRIMAXIN re-examined to determine whether it should be decreased or the antibiotic discontinued.

As with other antibiotics, prolonged use of PRIMAXIN may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken. While PRIMAXIN possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system function during prolonged therapy is advisable.

Drug Interactions—Since concomitant administration of PRIMAXIN and probenecid results in only minimal increases in plasma levels of imipenem and plasma half-life, it is not recommended that probenecid be given with PRIMAXIN.

PRIMAXIN should not be mixed with or physically added to other antibiotics. However, PRIMAXIN may be administered concomitantly with other antibiotics, such as aminoglycosides.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Gene toxicity studies were performed in a variety of bacterial and mammalian tests *in vivo* and *in vitro*. The tests were: V79 mammalian cell mutation assay (PRIMAXIN alone and imipenem alone), Ames test (cilastatin sodium alone), unscheduled DNA synthesis assay (PRIMAXIN), and *in vivo* mouse cytogenicity test (PRIMAXIN). None of these tests showed any evidence of genetic damage.

Reproduction tests in male and female rats were performed with PRIMAXIN at dosage levels up to 8 times the usual human dose. Slight decreases in live fetal body weight were restricted to the highest dosage level. No other adverse effects were observed on fertility, reproductive performance, fetal viability, growth, or postnatal development of pups. Similarly, no adverse effects on the fetus or on lactation were observed when PRIMAXIN was administered to rats late in gestation.

Pregnancy—Pregnancy Category C: Teratogenicity studies with cilastatin sodium in rabbits and rats at 10 and 33 times the usual human dose, respectively, showed no evidence of adverse effect on the fetus. No evidence of teratogenicity or adverse effect on postnatal growth or behavior was observed in rats given imipenem at dosage levels up to 30 times the usual human dose. Similarly, no evidence of adverse effect on the fetus was observed in teratology studies in rabbits with imipenem at dosage levels at the usual human dose.

Teratology studies with PRIMAXIN at doses up to 11 times the usual human dose in pregnant mice and rats during the period of major organogenesis revealed no evidence of teratogenicity.

Data from preliminary studies suggest an apparent intolerance to PRIMAXIN (including emesis, inappetence, body weight loss, diarrhea, and death) at doses equivalent to the average human dose in pregnant rabbits and cynomolgus monkeys that is not seen in non-pregnant animals in these or other species. In other studies, PRIMAXIN was well tolerated in equivalent or higher doses (up to 11 times the average human dose) in pregnant rats and mice. Further studies are under way to evaluate these findings.

There are, however, no adequate and well-controlled studies in pregnant women. PRIMAXIN should be used only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRIMAXIN is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in infants and children below 12 years of age have not yet been established.

Adverse Reactions: PRIMAXIN is generally well tolerated. Many of the 1,723 patients treated in clinical trials were severely ill and had multiple background diseases and physiological impairments, making it difficult to determine causal relationship of adverse experiences to therapy with PRIMAXIN.

Local Adverse Reactions—Local adverse clinical reactions that were reported as possibly, probably, or definitely related to therapy with PRIMAXIN were: phlebitis/thrombophlebitis (3.1%), pain at the injection site (0.7%), erythema at the injection site (0.4%), vein induration (0.2%), infused vein infection (0.1%).

Systemic Adverse Reactions—The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to PRIMAXIN were: nausea (2.0%), diarrhea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%) (see PRECAUTIONS), dizziness (0.3%), pruritus (0.3%), urticaria (0.2%), somnolence (0.2%).

Additional adverse systemic clinical reactions reported as possibly, probably, or definitely drug related occurring in less than 0.2% of the patients or reported since the drug was marketed are listed within each body system in order of decreasing severity: *Gastrointestinal*—pseudomembranous colitis (see WARNINGS), hemorrhagic colitis, gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, heartburn, pharyngeal pain, increased salivation; *CNS*—encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, psychic disturbances; *Special Senses*—transient hearing loss in patients with impaired hearing, tinnitus; *Respiratory*—chest discomfort, dyspnea, hyperventilation, thoracic spine pain; *Cardiovascular*—palpitations, tachycardia; *Renal*—oliguria/anuria, polyuria; *Skin*—erythema multiforme, facial edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae; *Body as a Whole*—polyarthralgia, asthenia/weakness.

Adverse Laboratory Changes—Adverse laboratory changes without regard to drug relationship that were reported during clinical trials or reported since the drug was marketed were: *Hepatic*—increased SGPT, SGOT, alkaline phosphatase, bilirubin, and LDH; *Hemic*—increased eosinophils, positive Coombs test, decreased WBC and neutrophils, including agranulocytosis, increased WBC, increased platelets, decreased platelets, decreased hemoglobin and hematocrit, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils; *Electrolytes*—decreased serum sodium, increased potassium, increased chloride; *Renal*—increased BUN, creatinine; *Urinalysis*—presence of urine protein, urine red blood cells, urine white blood cells, urine casts, urine bilirubin, and urine urobilinogen.

NOTE: Due to the high antimicrobial activity of PRIMAXIN, it is recommended that the maximum total daily dosage not exceed 50 mg/kg/day or 4.0 g/day, whichever is lower.

How Supplied: PRIMAXIN is supplied as a sterile powder mixture in vials, infusion bottles, and single-dose ADD-Vantage®[†] vials containing imipenem anhydrous and cilastatin sodium as follows: 250 mg imipenem equivalent and 250 mg cilastatin equivalent; 500 mg imipenem equivalent and 500 mg cilastatin equivalent.

Caution: The suspension from vials is not for direct infusion.

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[*] when indicated organisms are suspected at indicated sites

January 1988
Volume 207, Number 1

Annals of
Surgery

The Kaplan and Meier and the Nelson Estimate for the Probability of Ulcer Recurrence 10 and 15 Years after Parietal Cell Vagotomy

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From the Surgical Department 1, Kommunehospitalet, Copenhagen, Denmark

The use of a nonparametric estimate from incomplete observations is demonstrated on ulcer recurrence 10–15 years after parietal cell vagotomy in 339 patients with duodenal ulcer. The median period of observation was 108 months (range: 1–197 months). Proven recurrent ulcer developed in 62 patients. The life-table method as described by Kaplan and Meier and Nelson's modification are demonstrated. The calculated risk of recurrence after 10 years was 23% (±3.8%) and after 15 years was 27% (±4.3%). The rate of recurrence seemed to decline toward the end of the trial time.

NONPARAMETRIC ESTIMATION from incomplete observation is often used in clinical trials that study time until death (clinical trials of cancer therapy). It is, however, equally relevant to use the estimate in trials that study time until other types of untoward events.

Medical follow-up trials often deal with incomplete follow-up data due to either accidental or controlled losses. Complete follow-up data on all patients is the ideal situation and would give the true rate of the event studied. The major advantage of nonparametric estimation from incomplete observation is that the method makes it possible to use all information from the trial accumulated up to the end of the study.

This paper presents the use of nonparametric estimates from incomplete observation and demonstrates the results from the same study, first followed for 10 years and then again after 15 years.

Patients and Methods

In January 1969, parietal cell vagotomy without drainage was first introduced as the surgical treatment of patients with a duodenal ulcer.[1,2] In 1983, we reported the follow-up results, 2–12 years after surgery, of the patients in the Copenhagen study.[3] In the current study we extended the follow-up period of the same patients, all treated between 1969 and 1979.

Three hundred fifty patients had elective parietal cell vagotomy because of a chronic ulcer located in the duodenal bulb, the pylorus, or the prepyloric area. Information concerning operative technique, acid secretion test,

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Submitted for publication June 1, 1987.

TABLE 1. *Example of Formulas Computing the Kaplan and Meier and Nelson Estimates*

Time for Event	Numbers at Risk at t_i	Risk in Interval	Nelson Estimate $\hat{B}(t_1)$	Kaplan Estimate $\hat{S}(t_1)$	SD of $\hat{B}(t_i)$ SD $(\hat{B}(t_1))$	SD of $\hat{S}(t_1)$ SD $(\hat{S}(t_1))$
t_i	$N(t_i)$	$1/N(t_i)$	$\Sigma \frac{1}{N(t_i)}$	$\pi\left(1 - \frac{1}{N(t_i)}\right)$	$\Sigma \frac{1}{N(t_i)^2}$	$\hat{S}(t_i)^*$ SD $(\hat{B}(t_i))$
1	10	0.1	0.1	0.9	0.1	0.09
5	8	0.125	0.225	0.788	0.16	0.126
9	6	0.167	0.392	0.656	0.23	0.151

distribution of age, sex, and site of ulcer is previously described.[3] All patients without known recurrent ulcer were traced *via* the National Register, and follow-up examination was done between April 1985 and May 1986.

Eleven patients were excluded from the analysis owing to a lack of follow-up information. Thus, a total of 339 patients remained for the analysis. After completion of the follow-up examination, seven patients did not respond, but using the Kaplan and Meier estimate, these patients are included using the previous known time of follow-up examination.

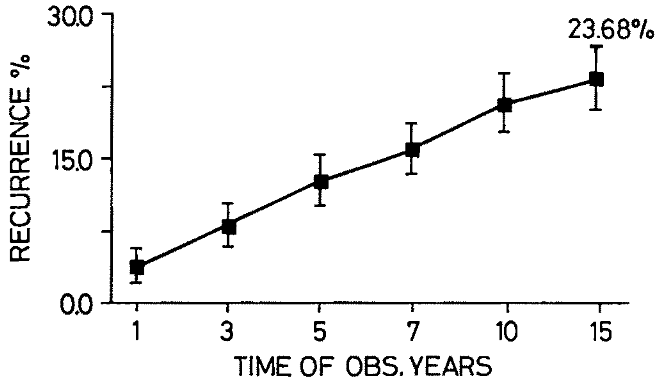

FIG. 1. Probability of ulcer recurrence after parietal cell vagotomy. Kaplan-Meier plots ± 1 SD.

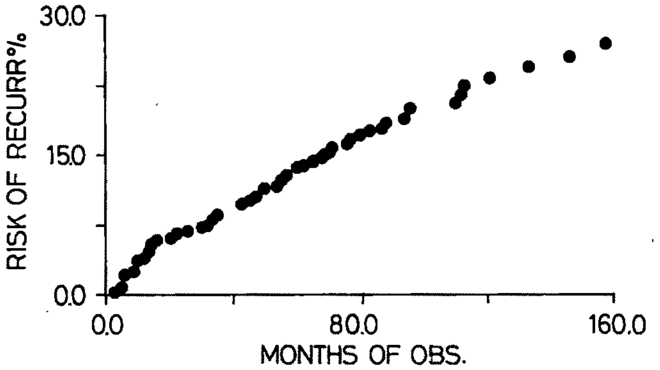

FIG. 2. Integrated recurrence risk after parietal cell vagotomy. Nelson plots ± 1 SD.

Clinical Follow-up

All patients alive without known recurrence with follow-up information of longer than 3 months were sent a similar questionnaire as at the 1981 follow-up examination. Primary nonresponders were sent a additional questionnaire. Secondary nonresponders were, if possible, contacted by telephone. Reports on examinations for ulcer symptoms by general practioners or hospitals were obtained. The median observation time was 108 months (range: 1–197 months).

Statistical Analysis

The ulcer recurrence probability was calculated with due regard to the incomplete follow-up information. The actuarial or life table method as described by Kaplan and Meier[4] was used. Since it is more common to speak of the risk of ulcer recurrence than the freedom from recurrence, data are given as the probability of ulcer recurrence within a given period.

To demonstrate a possible variation in the risk of recurrence over a short period, Nelson's modification of the actuarial method[5] was used. This gives the integrated ulcer recurrence rate as a function of time.

References describing nonparametric estimate for incomplete data are given,[4–7] but to show how simple the analysis is and at the same time perhaps to enable physicians who do not have statistical training to use the method, the method of analysis used for this paper is depicted in Table 1.

TABLE 2. *The Kaplan and Meier and Nelson Estimates for Ulcer Recurrence after Parietal Cell Vagotomy for the 1981 and 1986 Follow-up Study*

	1981	1986
Kaplan and Meier estimate		
10 years	23.76 ± 4.38	20.85 ± 3.03
15 years	?	23.68 ± 3.33
Nelson estimate		
10 years	26.76 ± 5.78	23.31 ± 3.83
15 years	?	26.92 ± 4.37

Results

Of the 339 patients studied, 62 (18.3%) had an ulcer recurrence. The probability of ulcer recurrence, calculated by means of the acturial method, is shown in Figure 1. After 10 years, the risk of recurrence was 20.85% ± 3.03% (mean ± 1 SD), and after 15 years was 23.68% ± 3.33% (mean ± 1 SD).

The integrated estimate for ulcer recurrence is shown in Figure 2. After 10 years, the risk of recurrence was 23.31% ± 3.83% (mean ± 1 SD), and after 15 years was 26.92% ± 4.37% (mean ± 1 SD). There seems to be a higher risk at the beginning, then almost a constant risk and possibly a slight decline in the recurrence risk toward the end of the trial.

Discussion

The 10-year follow-up examination of The Copenhagen parietal cell vagotomy study[3] and the current 15-year follow-up examination were carried out using the exact same method. The results of both the Kaplan and Meier estimate and the Nelson estimate for recurrence after the two follow-up studies are shown in Table 2. Graphic presentation of the Kaplan and Meier estimate for recurrence after the two follow-up studies is shown in Figure 3. The number of recurrences has risen from 42 (13%) to 62 (18%). In the 1981 study, the actuarial probability of ulcer recurrence after 10 years was 23.76% ± 4.38% and the corresponding integrated risk was 26.76% ± 5.78%. In 1981, the Nelson estimation showed a constant monthly risk of 0.23%, and therefore we could expect a probability rate of approximately 37% after 15 years. However, with additional follow-up study from 10 to 15 years, the estimated probability rate showed a rate of 23.68% ± 3.33%.

The median 1981 observation time was 48 months (range: 1–128 months) and the current 1986 observation time was 108 months (range: 1–197 months), which is reflected in the Kaplan and Meier and Nelson estimates giving smaller standard deviation of mean and therefore a higher accuracy of the estimates of recurrence.

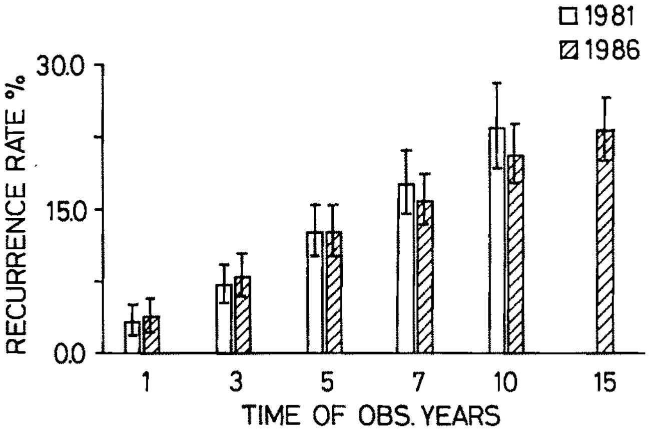

FIG. 3. Probability of ulcer recurrence after parietal cell vagotomy, the 1981 and 1986 follow-up studies. Kaplan-Meier plots ± 1 SD.

The Copenhagen parietal cell vagotomy study has now been followed for a considerably long time. The plot of the Nelson estimates shows the risk of having a recurrent ulcer as a function of time. It seems that the risk is decreasing toward the end of trial time, therefore we can hope that the probability of ulcer recurrence after parietal cell vagotomy without drainage for a chronic duodenal ulcer has reached a stable value of around 25%. However, the final true rate of recurrence can be obtained only with complete follow-up study of all patients. The additional 5 years of trial time from 10 to 15 years has helped us, using the Kaplan and Meier and the Nelson methods to give a more reliable estimate of both the rate and the risk of recurrence.

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Incidence of Perforated and Bleeding Peptic Ulcers before and after the Introduction of H2-Receptor Antagonists

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The incidence of perforated and bleeding peptic ulcer requiring emergency surgery was studied in a defined population before and after the introduction of histamine H2-blockers. The incidence of these ulcer complications was unchanged from 1974 to 1984 with an incidence of ulcer perforation from 4 to 10/100,000 per year and of bleeding ulcer from 5 to 10/100,000, indicating that the H2-blockers have not changed the incidence of severe ulcer complications.

FOLLOWING THE INTRODUCTION of H2-blockers in the treatment of peptic ulcer disease, there has been a sharp decrease in elective ulcer surgery.[1-4] The number of operations for perforated ulcer in this period has been almost constant[3,5,6] or slightly decreased,[4,7] although some reports from England and Scotland have shown an increase after 1977.[8,9] The changes in surgery for bleeding gastroduodenal ulcer in this period apparently have not been investigated.

The current study deals with the incidence of surgery for perforated and bleeding gastroduodenal ulcers in a defined population before and after the introduction of histamine H2-blockers.

Materials and Methods

Based on a population of approximately 210,000, the number of operations for perforated and bleeding ulcer from 1974 to 1984 was studied. Cimetidine has been available in Denmark since September 1977. The hospital serves a well-defined area of Copenhagen, and as a result of the organization of the Danish health care and hospital system, all patients from this area are admitted to this hospital for emergency surgical conditions. In the 11-year period under study, the population increased by 7% to 212,010, the number of children (younger than 15 years) decreased from 28% to 20% of the population, whereas the number of persons of 65 years or older increased by 3% to 9.6% of the adult population. Median age for the adult population (≥15 years) increased in the period under study from 37.7 to 40.7 years. The sex ratio was constantly 1:1 throughout the period. To adjust for the demographic changes, operation rates were calculated as the number of operations per 100,000 inhabitants older than 14 years per year. For the age group 15–64 years and for those age 65 or older, the age-specific operation rates were calculated.

For statistical evaluation of differences in operation rates the Mann-Whitney U-test was used; p values less than 0.05 were considered significant.

Results

During the 11-year period, 118 operations for perforated ulcer were performed (Fig. 1). The sex ratio (m:w) was 1.8:1 and the median age was 50 years (range: 22–93 years). No significant change in the operation rates before and after 1977 was found when the material was analyzed as a whole, or when it was analyzed for operations on men and women separately for duodenal and gastric (including prepyloric) ulcers or for age-specific operation rates for patients from 15 to 64 years and for those 65 years or older (Fig. 2).

The annual operation rates for 107 patients who had surgery for bleeding ulcer are shown in Figure 3. The sex ratio (m:w) was 2.5:1, and the median age was 56 years (range: 23–92 years). No significant change was found in the operation rates before and after September 1977. No changes could be demonstrated when the series was divided according to sex, age, and ulcer location (Fig. 4).

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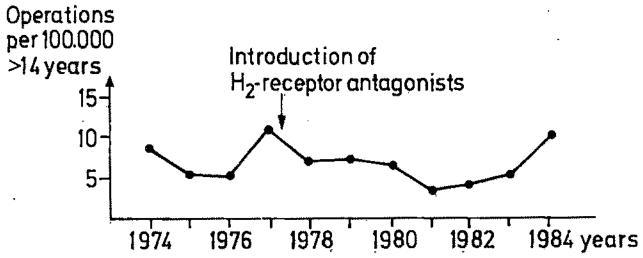

FIG. 1. Operation rates for perforated peptic ulcers from 1974 to 1984. The number of operations per 100,000 inhabitants 14 years or older is reflected.

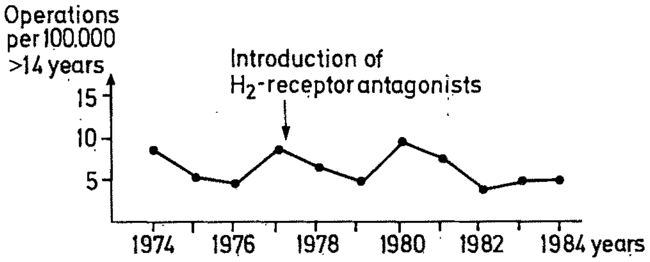

FIG. 3. Operation rates for bleeding peptic ulcers from 1974 to 1984. The number of operations per 100,000 inhabitants older than 14 years is reflected.

Thirteen per cent of patients with perforated ulcer and 43% of patients with bleeding ulcer operated on after 1978 had been treated with cimetidine before admission. Regular use of nonsteroid anti-inflammatory drugs (NSAID) was found in 30% of patients with perforated ulcer before 1977 and in 37% after 1977 compared with 36% and 42%, respectively, of patients operated on for bleeding ulcer ($p > 0.05$).

Discussion

Operation rates for severe ulcer complications, perforation, and hemorrhage were found to be unchanged after the introduction of H2-blockers. Since no changes have taken place in the indications for surgery of bleeding ulcer, the calculated operation rates show the true development in ulcer surgery for perforated and bleeding gastroduodenal ulcers in this period.

Previous studies have shown that almost half of the patients with perforated gastroduodenal ulcers[7,10] and about 20% of those with hemorrhage[11] had an ulcer history of less than 3–4 weeks, which probably explains the findings in the current study that only 13% of patients with perforated ulcer and 43% of patients with bleeding ulcer had received H2-blockers after 1977.

During later years new trends in the occurrence of ulcer complications have become apparent, since there has been an increased number of older patients and of

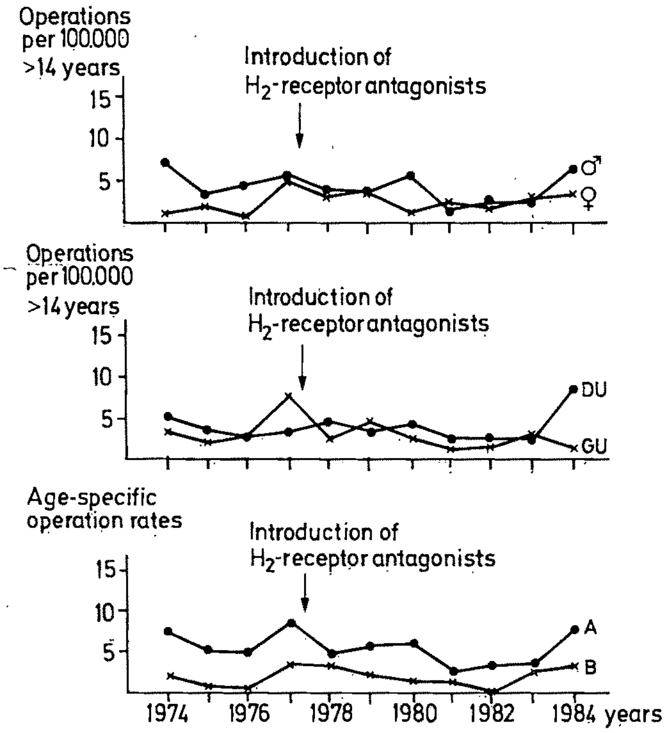

FIG. 2. Operation rates for perforated peptic ulcers from 1974 to 1984 in relation to sex, ulcer location, and age. DU = duodenal ulcer. GU = gastric ulcer. A = operations per 100,000 inhabitants 15–64 years old. B = operations per 100,000 inhabitants older than 65 years.

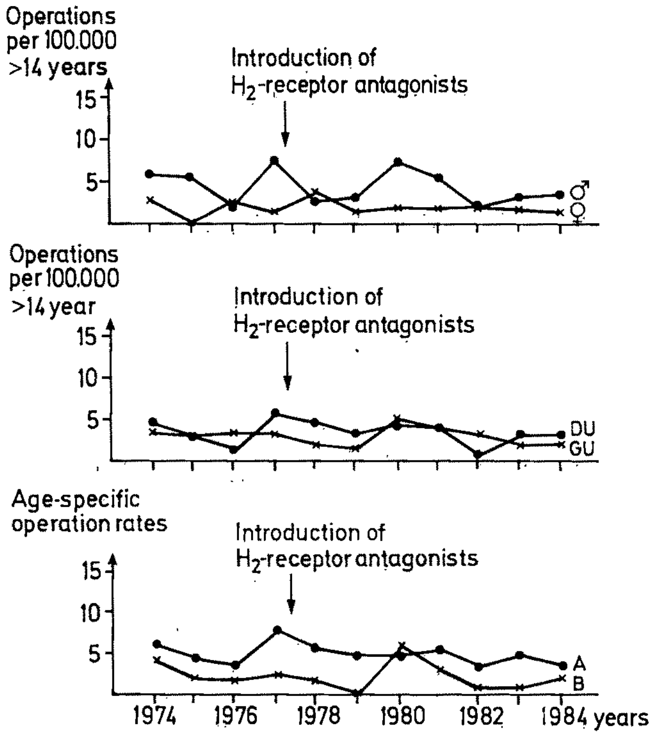

FIG. 4. Operation rates for bleeding peptic ulcer from 1974 to 1984 according to sex, ulcer location, and age. DU = duodenal ulcer. GU = gastric ulcer. A = operations per 100,000 inhabitants 15–64 years old. B = operations per 100,000 inhabitants older than 65 years.

women and a decrease in the incidence of perforation in the younger age groups.[6,12] These trends have been explained by the increasing life expectancy of women as well as by the increase in the use of ulcerogenic antirheumatic drugs especially among elderly women.[5,12] This age and sex difference is not obvious in the current study, although there is a tendency towards a more even sex distribution (2.3:1 before 1977 compared with 1.4:1 after 1977). A similar trend is observed for bleeding ulcer (3.1:1 before 1977 compared with 2.0:1 after 1977).

The use of NSAID is one of the factors generally considered to be of importance in the development of perforated and bleeding ulcers.[5,12–14] The use of NSAID by patients who had emergency surgery for ulcer complications was, however, unchanged in the period under study, and thus cannot explain that no decrease occurred in the incidence of surgery for perforation and hemorrhage. Whether other ulcerogenic factors have changed in this period is uncertain, but can hardly have had more than a marginal influence.

In conclusion, the introduction of H2-blockers has not decreased the incidence of severe ulcer complications requiring emergency surgery, indicating that these drugs probably will have no influence on mortality from peptic ulcer disease.

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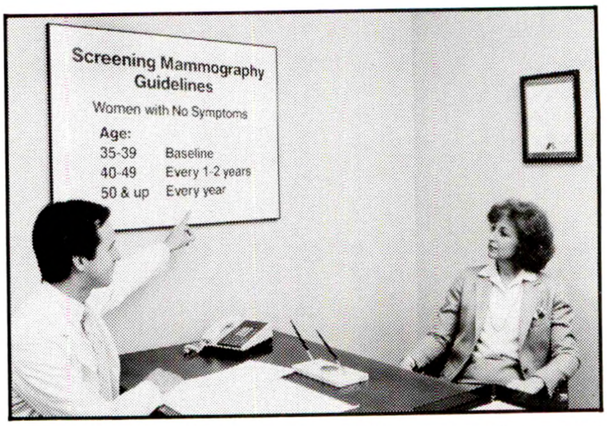

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Postoperative Complications and Mortality after Surgery for Gastric Cancer

ASGAUT VISTE, M.D., TROND HAUGSTVEDT, M.D., GEIR EGIL EIDE, CAND. REAL., ODD SØREIDE, M.D., and THE NORWEGIAN STOMACH CANCER TRIAL MEMBERS

Complication rates and postoperative mortality were studied in 1010 consecutive patients entered into the Norwegian Stomach Cancer Trial. Twenty-eight per cent of the patients had one or more complications (31% of the men and 21% of the women). General complications (pneumonia, thromboembolic, and cardiac) were most frequent. The postoperative mortality rate for resected patients was 8.3% (63 of 763). Complication and mortality rates were highest for proximal resections (52% and 16%) followed by total gastrectomy (38% and 8%), subtotal resection (28% and 10%), and distal resection (19% and 7%). By logistic regression analysis it was found that age, sex, operative procedure, prophylactic antibiotics, and splenectomy were significantly related to postoperative complications. The odds ratio for complication for men *versus* women was 1.75: for no antibiotics *versus* antibiotic prophylaxis it was 2.5. Relative to distal resection the odds ratio for complications after subtotal resection was 2.2, for total gastrectomy was 3.9, and for proximal resection was 7.6. Age and sex were the only factors that affected operative mortality. The odds ratio for mortality for men *versus* women was 2.3. The odds ratio for operative mortality was 2.2 when the age of the patient increased with 10 years.

DESPITE IMPROVEMENTS IN diagnostics, pre-, intra-, and postoperative care and surgical technique, the complication rate after surgery for gastric malignancy has virtually remained unchanged during the last two decades.[1-4] Complication rates of 20–40% and hospital mortality rates of 10–33% are commonly reported in Western series,[1,5-7] which contrast a mortality rate of 2–3% reported from Japan.[8,9] It seems that extensive procedures, such as total gastrectomy, carry a higher complication rate than partial resections.[1,3-5] Consequently, the extensive operation must be followed by an improved long-term survival advantage to be justified.

From the Department of Surgery, Section for Medical Informatics and Statistics, University Hospital of Bergen, Bergen, Norway, and the Norwegian Stomach Cancer Trial

Some studies indicate that a survival advantage for extensive gastric resections as compared to less radical procedures may be achieved if the high postoperative morbidity and mortality rates after the former operation can be reduced.[10,11] A reduction in the complication rate may be attained if factors related to complications are identified. So far, little is known about clinical and operative factors related to postoperative morbidity and mortality.

The purpose of this paper was to analyze predisposing factors related to postoperative complications and mortality after gastric surgery for cancer. Further, it was our intention to study a possible relation between complication rates and hospital level to identify the effect of level of care on morbidity and mortality.

Patients and Methods

The Norwegian Stomach Cancer Trial is organized as a prospective observational study with 51 surgical units participating. The patient accrual started September 1, 1982. By December 31, 1984, 1165 patients (705 men and 460 women) had been included. These patients represent 54% of all patients with stomach cancer registered by the Cancer Registry of Norway during the same period. The participating hospitals submitted information on each patient recorded on data sheets to the study headquarters at the University Hospital in Bergen for punching and subsequent analyses.

Of the 1165 patients entered, 1010 (87%; 608 men and 402 women) underwent surgery and 763 patients (65%) had a resection.

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TABLE 1. *Complications for 1010 Patients Operated On for Stomach Cancer*

	No. of Complications*	Per cent of Patients Operated On
Intestinal obstruction	15	1
Postoperative hemorrhage	25	2
Anastomotic insufficiency†	41	4
Intra-abdominal infection	37	4
Wound infection	37	4
Wound dehiscence	12	1
Septicemia	42	4
General complications‡	177	18
No complications	722	72

* Some patients had more than one complication.
† Demonstrated on routine x-ray studies at 5–7 days after operation.
‡ Cardiac, pulmonary, thromboembolism, etc.

Pre- and intraoperative variables that may be related to postoperative complications and mortality were cross-tabulated and analyzed with chi-square statistics. The following factors were considered: age (18–59, 60–69, 70–79, 80–91 years), sex, hospital level (University, County, local), preoperative weight loss (≤5 kp, ≥6 kp), operative procedure, operative evaluation (curative *vs.* palliative resection), splenectomy, prophylactic antibiotics, anastomotic technique (stapler *vs.* hand-sutured), and stage of the disease (TNM classification[12]).

Postoperative mortality was defined as all deaths related to postoperative complications as specified on the registration forms, irrespective of whether the patients died before or after 30 days after operation.

To further analyze interactions between variables related to complications and mortality, we performed a backward stepwise logistic regression analysis,[13] taking into account all possible second-order interactions. By this approach we could study the effect on the dependent variable (*i.e.*, complications and mortality) of one particular variable, whereas all other variables were held constant. Separate analyses were performed with complications and mortality as dependent variables, respectively. The logistic regression analysis was restricted to patients having a resection (763 patients). In the logistic regression analysis, age was included as a continuous variable

The final regression model should fulfill the following three requirements: (1) the model should fit the ob-

TABLE 2. *Complications and Mortality by Type of Operation for 1010 Patients Treated for Stomach Cancer*

	Complications	Mortality
	No. of Patients (%)	No. of Patients (%)
Total gastrectomy (N = 350)	134 (38)	27 (8)
Subtotal gastrectomy (N = 151)	42 (28)	15 (10)
Proximal resection (N = 31)	16 (52)	5 (16)
Distal resection (N = 231)	43 (19)	16 (7)
Gastroenterostomy (N = 72)	16 (22)	7 (10)
Fistulas, tubes, etc. (N = 17)	4 (24)	1 (6)
Explorative laparotomy (N = 158)	21 (13)	5 (3)

TABLE 3. *Complications and Operative Mortality by Sex, Age, Preoperative Weight Loss, Prophylactic Antibiotics, Splenectomy, Anastomotic Technique, and Hospital Level for 763 Patients Resected for Stomach Cancer*

	Complication	Mortality
	No. of Patients (%)	No. of Patients (%)
Sex		
Men	163/461 (35.4)	45/463 (9.7)
Women	72/298 (24.2)	18/299 (6.0)
Not stated	4	2
Age		
≤59 years	27/146 (18.5)	2/145 (1.4)
≤69 years	74/219 (33.8)	12/221 (5.4)
≤79 years	98/288 (34.0)	33/289 (11.4)
≥80 years	36/106 (34.0)	16/107 (15.0)
Not stated	4	1
Weight loss		
≤5 kg	119/361 (33.0)	24/362 (6.6)
≥6 kg	69/218 (31.7)	22/219 (10.0)
Not stated	184	182
Prophylactic antibiotics		
Yes	160/550 (29.1)	43/554 (7.8)
No	68/187 (36.4)	18/186 (9.7)
Not stated	26	23
Anastomotic technique		
Staplers	113/311 (36.3)	26/310 (8.4)
Hand sutures	119/440 (27.0)	36/442 (8.1)
Not stated	12	11
Splenectomy		
Yes	109/260 (41.9)	22/261 (8.4)
No	125/493 (25.4)	39/495 (7.9)
Not stated	10	7
Hospital level		
University	110/234 (34.0)	18/326 (5.5)
County	33/165 (20.0)	13/165 (7.9)
Local	91/269 (33.8)	32/270 (11.9)
Not stated	5	2
Stage of disease (TNM)		
I	24/99 (24.2)	3/98 (3.1)
II	68/185 (36.8)	17/185 (9.2)
III	107/340 (31.5)	33/344 (9.6)
IV	23/94 (24.5)	4/94 (4.3)
Not stated	45	42

TABLE 4. *P Values Revealed by Cross-tabulations and Statistical Analysis (Chi-Square Statistics)*

	Complication (p value)	Mortality (p value)
Age	0.004	0.001
Sex	0.001	0.07
Hospital group	0.003	0.02
Preoperative weight loss	0.74	0.14
Surgical procedure	0.001	0.29
Splenectomy	0.001	0.79
Prophylactic antibiotics	0.06	0.41
Anastomotic technique	0.007	0.91
Operative evaluation	0.74	0.89
Stage of disease (TNM)	0.08	0.08

TABLE 5. *Odds Ratios for Postoperative Complications as Estimated from the Logistic Regression Analysis*

Variable Categories	Odds Ratios	p Value	95% CI
Sex		0.002	
Women	1		
Men	1.75		1.22–2.52
Age		0.0001	
x	1		
x + 10	1.59		1.31–1.92
Surgical procedure		0.0001	
Distal resection	1		
Subtotal resection	2.24		1.32–3.79
Total gastrectomy	3.74		2.18–6.42
Proximal resection	7.23		3.00–17.42
Prophylactic antibotics		0.0001	
Given	1		
Not given	2.42		1.59–3.69
Concomittant splenectomy		0.01	
No	1		
Yes	1.73		1.13–2.65

served data adequately, *i.e.*, give a Hosmer's test of fit with $p > 0.05$[14]; (2) to adjust for multiple significance testing, a significance level for each variable of 0.01 rather than 0.05 was applied as a stopping criterion,[15] thus reducing the overall probability of Type I error to an acceptable level; (3) the final model should explain the effect of individual variables on complications or mortality in the simplest way (most parsimonious model[16]).

The computations were performed by the BMDP[14] statistical program package implemented on the Univac 1100 computer at the University of Bergen.

Results

Overall Results

The number of complications encountered in the 1010 patients operated on are given in Table 1. The overall complication rate was 28%: 31% for men and 21% for women. General complications (pulmonary, thromboembolic, and cardiac) were most frequently found.

Postoperative complications and mortality according to operative procedure are given in Table 2. The complication rate was highest for proximal resection (52%) followed by total gastrectomy (38%), subtotal resection (28%), and distal resection (19%). The operative mortality for all resected patients was 8.3% (63 of 763): 16% for patients having a proximal resection, 10% following subtotal resection, 8% for total gastrectomy, and 7% for distal resection.

Resected Patients

Patients resected for cure had a complication rate of 30.9% (177 of 573) and a mortality rate of 8.0% (46 of 574) *versus* 31.3% (57 of 182) and 9.2% (17 of 184) for patients having a palliative resection (no significant differences). The tumor stage (TNM classification) did not affect complication and mortality rates (Tables 3 and 4).

Cross-tabulations between postoperative complications and other pre- and intraoperative variables revealed statistically significant associations between the dependent variable complications and age, sex, hospital level, operative procedure, splenectomy, and anasto-

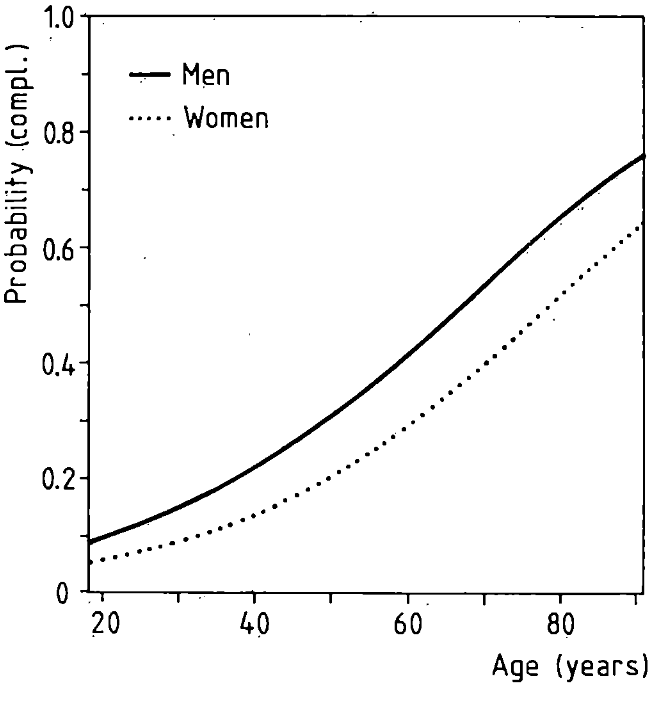

FIG. 1. Probability of postoperative complication for men and women according to age.

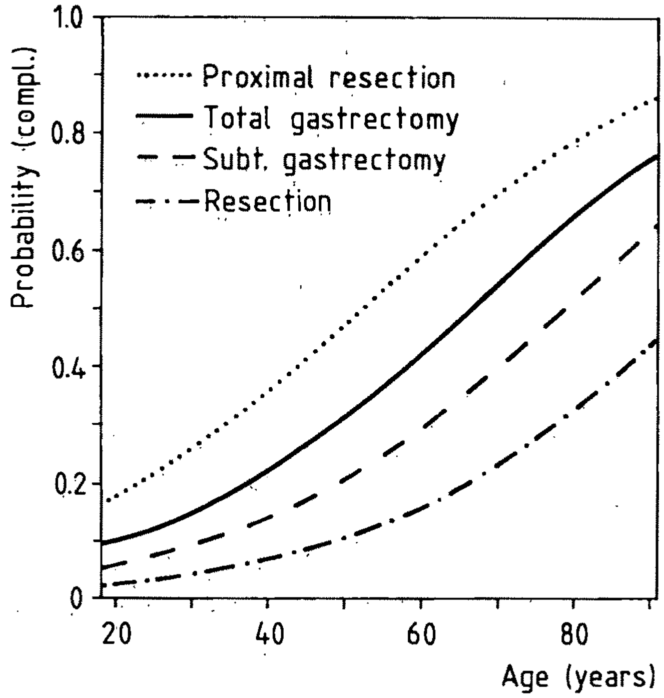

FIG. 2. Probability of complication after various operative procedures *versus* age.

motic technique. Further analyses revealed that age and hospital group were related to operative mortality (Tables 3 and 4).

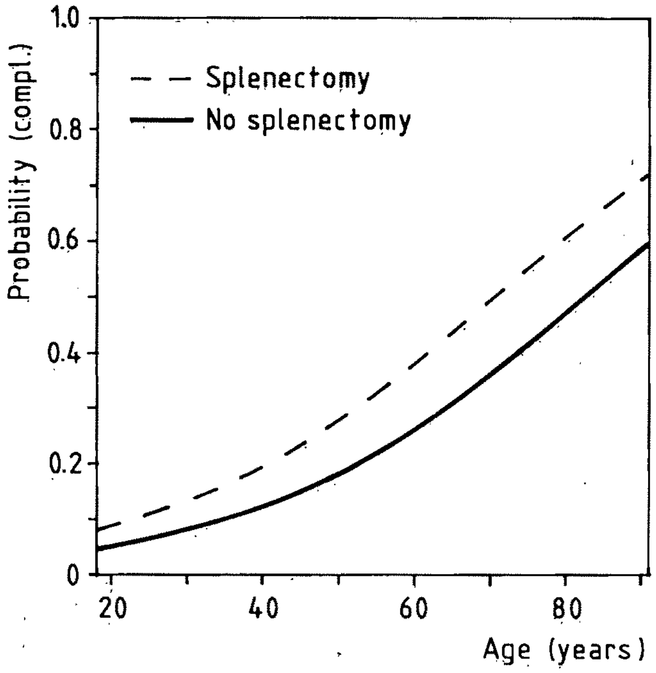

FIG. 3. Probability of complication after concomitant splenectomy *versus* age.

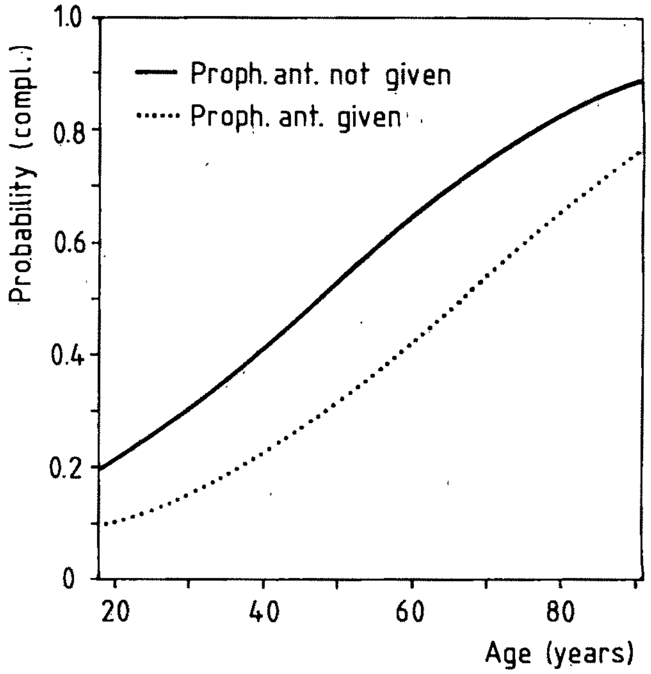

FIG. 4. Probability of complication related to administration of prophylactic antibiotics and according to age.

The final logistic regression model fitted the data well ($p = 0.33$ for goodness of fit). By this analysis we found that complications were significantly influenced by sex, age, operative procedure, prophylactic antibiotics, and splenectomy. Preoperative weight loss, anastomotic technique, operative evaluation, and stage of disease were not associated with complication rate, whereas hospital level was of borderline significance. The odds ratios with 95% confidence intervals and p values are given in Table 5. Men had a higher complication rate than women (estimated odds ratio of 1.75). For operative procedures, the lowest complication risk was found after distal resection, whereas proximal resection carried the highest odds ratio, *i.e.*, 7.2 times higher than the former. Based on the final logistic regression model we plotted the variables operative procedure, prophylactic

TABLE 6. *Odds Ratios for Operative Mortality for 763 Patients Operated On for Stomach Cancer*

Variable	Odds Ratio	p Value	95% CI
Sex		0.005	
Women	1		
Men	2.33		1.26–4.31
Age		0.0001	
x	1		
x + 10	2.24		1.61–3.13

antibiotics, sex, and splenectomy against age, and the results are given in Figures 1–4.

The logistic regression analysis was repeated with operative mortality as the dependent variable. The final model (which fitted the data well; $p = 0.43$) revealed that sex ($p < 0.001$) and age ($p < 0.001$) were the only variables that independently influenced postoperative death. The results are visualized in Figure 5. Men had a higher postoperative mortality rate than women. Postoperative mortality increased almost exponentially with age.

Discussion

Several strategies should be explored to improve survival after surgery for gastric cancer. A reduction in operative mortality for patients undergoing a potential curative resection would clearly be beneficial, and interest should be focused on studies aimed at identification of pre- and intraoperative variables which are linked to postoperative complications and mortality. Factors assumed to predispose to complications include technical skill of the surgeon, operating time, malnutrition and age, prophylactic antibiotics as well as operative procedure performed.[17,18]

Most studies on complications after gastric surgery analyze possible predictive factors in a univariate manner, not taking the multivariate nature of this problem into account.[17–20] The limitations of such analyses are illustrated by the two-way cross-tabulations summarized in Table 4, which revealed six factors associated with complications and two related to postoperative mortality. However, the multivariate analyses reduced the number of true significant associations. More importantly, the multivariate analyses also identified variables clearly associated to complications that were not demonstrated by simple cross-tabulation and chi-square statistical analyses, as demonstrated for the variable prophylactic antibiotics (Tables 4 and 5). The reason for this discrepancy might be explained by interactions between the variables. Such findings also suggest that conclusions drawn on the basis of simple cross-tabulations and statistical analyses should be interpreted with care.

Previous studies have shown increasing complication and mortality rates with age,[21,22] whereas others have challenged this finding.[18] In the current study, age was a major determinator with respect to postoperative complication and mortality (Figs. 1–5). Further, men had higher risks than women for all types of complications such as anastomotic leak and bleeding, as well as general complications. A higher postoperative mortality rate for men than for women has also been demonstrated by Miwa,[23] but so far, no hypothesis has been proposed that can explain this finding. Detailed analyses of our data have not uncovered any mechanism that might explain the clear excess risk for men undergoing gastric surgery for cancer.

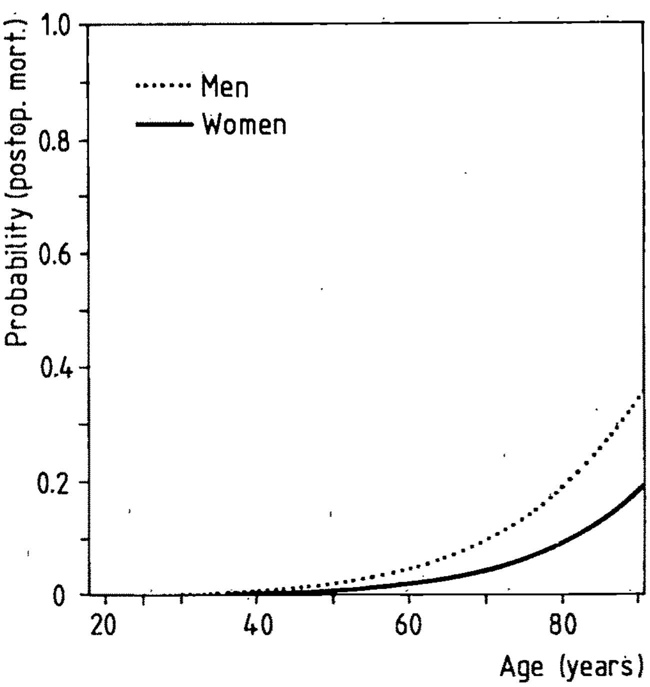

FIG. 5. Probability of operative mortality for men and women according to age.

As reported by others[1,24] we found that the type of operation affected the complication rate, *i.e.*, was higher for extensive procedures (like total gastrectomy) than for distal resection. This is an important conclusion as a potential increase in postoperative long-term survival is expected to follow more extensive operations. However, the survival advantage of an extensive operation performed *de principe* is still a matter of discussion.[25,26]

Some surgeons suggest that a minor surgical procedure as proximal resection for upper-third tumors is the treatment of choice. However, for the last two decades it has been known that proximal resection carries a higher complication rate than total gastrectomy.[1,3,10,24] This finding was confirmed in the current study, which demonstrated alarmingly high complication risks (Fig. 2) for this procedure. It was noted that septic and general complications were especially common after proximal resection. We do not find proximal resection to be any easier to perform than a total gastrectomy, and we recommend the latter procedure for all proximal tumors.

Removal of the spleen *en bloc* with the gastric specimen has traditionally been part of a standard radical gastric resection for cancer. Recently it has been suggested that splenectomy might have a detrimental effect on survival.[27] However, other studies have not been able to confirm the negative effect of splenectomy.[28] In this study we found an increased rate of complication after splenectomy. Whether splenectomy was performed or not did not have any influence on operative mortality.

Administration of prophylactic antibiotics reduced postoperative complications by approximately 10% (Table 3 and Fig. 4). A full discussion about the value of antibiotic prophylaxis in gastrointestinal tract surgery is beyond the scope of this paper. However, based on our data we conclude that any gastric resection for cancer should be covered by prophylactic antibiotics.

Malnutrition has for a long time been recognized to be associated with increased complication and operative mortality rates.[22,29] In this study, weight loss did not have an influence on complications and mortality. The explanation behind this rather controversial conclusion is probably that malnourished patients most often have advanced disease not suitable for resection.

Resection for stomach cancer often implies major surgery for patients at an increased risk. For this reason it might be expected that the level of care would influence patient outcome. We were, however, not able to discover any association between hospital level, complication, and operative mortality. The figures were, however, of borderline significance, with a lower complication rate for county hospitals than for university and local hospitals.

The overall operative mortality rate of 8.3% for resected patients found in this study is in accordance with that of most reported studies from the Western world.[1,2,4,7] Further, it should be noted that the mortality rate after total gastrectomy was comparable to the mortality rate after distal resection (7.7% *vs.* 6.9%). Japanese results are, however, far better,[8,9] and we should aim at reduced operative mortality rates as this will have a substantial impact on long-time survival. The only factors found to predict mortality were sex and age, whereas operative procedure and hospital group were at the borderline of significance.

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Appendix

The following are participating surgical departments of The Norwegian Stomach Cancer Trial. Halden Sykehus (Dr. Ø.

Hansen), Sentralsykehuset for Østfold (Dr. K. Andenaes), Sarpsborg Sykehus (Dr. S. Skjeldal), Moss Sykehus (Dr. C. Wessel-Holst), Sentralsykehuset i Akershus (Dr. K. Solheim*), Baerum Sykehus (Dr. E. Omland), Rikshospitalet (Dr. A. Bergan*), Ullevål Sykehus (Dr. T. Gerner, Dr. J Stadaas*), Aker Sykehus (Dr. T. B. Harbitz, Dr. I. Liavaag*), Diakonissehusets Sykehus Lovisenberg (Dr. J. Hogniestad), Diakonhjemmets Sykehus (Dr. Ø. Havig), Hamar Sykehus (Dr. O. Leidal), Kongsvinger Sykehus (Dr. R. Uggerud), Tynset Sykehus (Dr. B. Norbye), Gjøvik Fylkessykehus (Dr. S. Aasen), Buskerud Sentralsykehus (Dr. S. Svane), Ringerike Sykehus (Dr. P Holme), Vestfold Sentralsykehus (Dr. O. Holter), Horten Sykehus (Dr. N. Kollevold), Sandefjord Sykehus (Dr. O. Ruistuen), Larvik Sykehus (Dr. B. Sundal), Telemark Sentralsykehus (Dr. G. Haarberg), Notodden Sykehus (Dr. A. Skauby), Aust-Agder Sentralsykehus (Dr. E. Stenehjem), Vest-Agder Sentralsykehus (Dr. B. I. Haug), Mandal Sykehus (Dr. P. E. Hansen), Farsund Sykehus (Dr. A. Nysted), Sentralsykehuset i Rogaland (Dr. R. Hoel), Fylkessykehuset i Haugesund (Dr. J. Heggebø), Haukeland Sykehus (Dr. B. Arnesjø,* Dr. C. W. Janssen*) Diakonissehjemmets sykehus, Haraldsplass (Dr. F. P. Gullaksen), Hospitalet Betanien (Dr. J. Thunold), Fylkessykehuset på Stord (Dr. O. Stray), Fylkessykehuset i Odda (Dr. K. Svendby), Fylkessykehuset på Voss (Dr. A. Reisaeter), Fylkessykehuset i Florø (Dr. O. Husebø), Laerdal Sykehus (Dr. Krogh Sørensen), Fylkessykehuset i Ålesund (Dr. N. Andersson), Fylkessykehuset i Volda (Dr. Y. Norderval), Fylkessykehuset i Molde (Dr. T. Hasselgård), Fylkessykehuset i Kristiansund N. (Dr. T. Tennøe), Regionsykehuset i Trondheim (Dr. H. Fjøsne), Orkdal Sanitetsforenings Sykehus (Dr. H. G. Erichsen), Innherred Sykehus (Dr. T. Bjerkeseth*), Sandnessjøen Sykehus (Dr. Ø. Ylvisaker), Gravdal Sykehus (Dr. O. Høstmaelingen), Narvik Sykehus (Dr. T. Teigan), Regionsykehuset i Tromsø (Dr. K. Nordstrand, Dr. J. A. Johnson*), Harstad Sykehus (Dr. G. Thorsen), Hammerfest Sykehus (Dr. E. Andersen), Kirkenes Sykehua (Dr. D. Rojahn). The Cancer Registry of Norway (Dr. E. Glattre*).

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* Member of the working party.

An Analysis of When Patients Eat after Gastrojejunostomy

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Eighty-five patients who underwent a gastrojejunostomy either alone or in conjunction with vagotomy or gastric resection were evaluated for the day of beginning an oral intake adequate enough to sustain nonoliguric output. This occurred on the average by the seventh to eighth postoperative day, by which time at least 78% of patients were consuming an adequate oral intake. Adequate liquid intake occurred on the average 5.3 days in the absence of vagotomy and 8.8 days in the presence of vagotomy. However, this significant difference is accounted for by the patients who had gastrojejunostomy with vagotomy. Vagotomy with antrectomy, antrectomy alone, and subtotal gastrectomy were not significantly different. The apparent influence of vagotomy on gastrojejunostomy may be due to a type II statistical error. However, 92% of patients who had vagotomy with pyloroplasty consumed adequate liquids by the seventh postoperative day compared with 56% of patients who had vagotomy with gastrojejunostomy.

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DELAYED GASTRIC EMPTYING is the most frequent immediate postoperative complication directly related to a gastroenteric anastomosis.[1] However, the definition of a postoperative delay in gastric emptying varies and thus the incidence also varies. Information about when patients are able to consume an adequate oral liquid intake after gastrojejunal anastomosis is difficult to find. In this study we examine this question and some factors that may predispose to a delay in gastric emptying.

Methods

The charts of all patients who underwent a gastrojejunal anastomosis with or without gastric resection or with or without vagotomy at the University Hospital of the SUNY Health Science Center at Syracuse and the Syracuse Veterans Administration Hospital were reviewed for the years 1979–1986. To qualify for analysis, the patients had to satisfy specific criteria. These include the absence of (1) carcinoma, perforation, peritonitis, or sepsis either before or after operation, (2) renal or respiratory or cardiac failure either before or after operation, (3) inflammatory bowel disease or insulin-dependent diabetes, (4) anastomotic leak and/or wound complications, (5) operative placement of either a prograde nasogastric or a retrograde jejunal tube *through* the anastomosis, (6) nonanastomotic bowel obstruction distal to the duodenum either before operation or in the immediate postoperative period, (7) emergent operation, (8) infection outside of the peritoneal cavity, and (9) hypokalemia. An additional criterion for inclusion into the study was access to an unrestricted intake of a liquid diet within 12 hours of passing flatus after operation. Forty-eight patients did not meet these criteria and were excluded from analysis unless stated specifically to the contrary. There was no operative mortality in patients who met the above criteria.

A data sheet was established before the study. The data sheet was designed to obtain specific information to answer specific questions to avoid random correlations that might appear as a result of statistical analyses. Information on the data sheets was entered into a data base computer file, the contents of which were rechecked against the original patient records to ensure accuracy. Three patient records did not contain the information required and were excluded from analysis.

Adequate oral liquid intake was prospectively defined as consumption of enough liquid to maintain a urinary output of greater than 480 ml/24 h for the rest of the patient's required hospitalization. However, three

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fourths of the patients were still receiving intravenous fluids when they started oral intake. If the intravenous fluids were continued for more than 24 hours for any reason after the start of what appeared to be an adequate oral intake, the patient was not included in the analysis. This criterion resulted in the exclusion of an additional 17 patient records. If a patient met the definition of adequate oral intake while still receiving intravenous fluids within 24 hours of starting oral fluids, the patient had to continue to meet the requisite urinary output after discontinuation of the intravenous line in order to continue to qualify for adequate intake. The requisite urinary output also had to be met when the patient was taking solid food, but no value was assigned to the adequacy of solid food intake.

Statistical analyses included frequency and independent t-test.

Results

Age, Sex, and Operation

The age of the patients ranged from 19 to 86 years with a mean (±SE) of 52.4 ± 1.9 years and a median and mode of 49 years. Forty-three patients were men and 42 were women. The various types of operations are shown in Table 1. There is a relatively large group of patients who underwent a gastrojejunostomy without an accompanying vagotomy. Eight patients in this group had prophylactic gastrojejunostomy done for what was erroneously diagnosed as carcinoma of the pancreas at the time of operation or duodenal obstruction due to chronic pancreatitis (these assessments are based on the subsequent clinical course extending 4–8 years after operation); three had duodenal obstruction related to prior operative trauma occurring at least 7.5 months previously; three had prior inadvertent vagotomy during operations for esophageal reflux at least 12 months previously; and three had prior vagotomy with a poorly functioning pyloroplasty performed at least 15 months previously.

Day of Liquid and Solid Intake

The mean postoperative day of starting an adequate oral liquid intake for the entire group of patients was 7.7 ± 0.9 and for solid intake it was 10.9 ± 1.1.

The cumulative frequencies of the postoperative days when liquid and solid intake were started and continued without difficulty are shown in Table 2. By the fourth postoperative day 29% of patients and by the seventh postoperative day 78% of patients were taking adequate liquids. In contrast, by the sixth postoperative day 28% of patients and by the eleventh day 78% of patients were taking solids. The mean difference in number of days between starting liquids and solids was 3.2 ± 0.4 and the difference was 3 days in 77% of the patients.

TABLE 1. *Operations Performed*

Type	*N*
Gastrojejunostomy	17
Vagotomy + gastrojejunostomy	16
Antrectomy	11
Vagotomy + antrectomy	26
Subtotal gastrectomy	15
Total	85

Obstruction Versus *No Obstruction*

The mean postoperative day of starting an adequate oral liquid intake for patients undergoing operation for obstruction was 6.5 ± 0.4 and for those without obstruction it was 8.3 ± 1.3. The mean difference is not significant.

The cumulative frequencies of the postoperative days when liquid and solid intake were started and continued without difficulty in patients with preoperative obstruction (28%) and no obstruction (78%) are shown in Tables 3 and 4. By the seventh postoperative day, an almost equal percentage of patients began a liquid diet (Table 3). By the ninth postoperative day, an almost equal percentage of patients began a solid diet (Table 4).

Vagotomy was performed in 11 of 24 patients with obstruction. There was no significant difference in terms

TABLE 2. *Cumulative Frequencies of Days Starting Liquid and Solid Intake for All Patients with Gastrojejunostomy*

Liquid Intake			Solid Intake		
Day	Cum %	Z Score*	Day	Cum %	Z Score*
3	8.2	−0.56	3	1.2	−0.82
4	29.4	−0.44	4	8.2	−0.71
5	55.3	−0.32	5	15.3	−0.61
6	69.4	−0.20	6	28.2	−0.51
7	77.6	−0.08	7	45.9	−0.40
8	83.5	−0.03	8	56.5	−0.30
10	87.1	0.27	9	69.4	−0.20
11	90.6	0.39	10	72.9	−0.10
12	91.8	0.51	11	77.6	0.01
22	95.3	1.69	12	78.8	0.11
23	97.6	1.81	13	82.4	0.21
39	98.8	3.70	14	84.7	0.32
65	100.0	6.77	16	85.9	0.52
			17	88.2	0.62
			20	91.8	0.93
			25	92.9	1.45
			27	94.1	1.65
			36	97.6	2.58
			39	98.8	2.89
			68	100.0	5.87

* Z score = SD below or above mean.

TABLE 3. *Cumulative Frequencies of Days Starting Liquid Intake*

	Obstruction N = 24		No Obstruction N = 61	
Day	Cum %	Z Score*	Cum %	Z Score*
3	4.2	−1.46	9.8	−0.54
4	16.7	−1.02	34.4	−0.43
5	33.3	−0.57	57.4	−0.33
6	62.5	−0.13	72.1	−0.23
7	75.0	0.31	78.7	−0.13
8	87.5	0.76	80.3	−0.03
9			82.0	0.07
10			86.9	0.17
11	100.0	2.08		
12			88.5	0.38
22			93.4	1.39
23			96.7	1.49
39			98.4	3.12
65			100.0	5.76

* Z score = SD below or above mean.

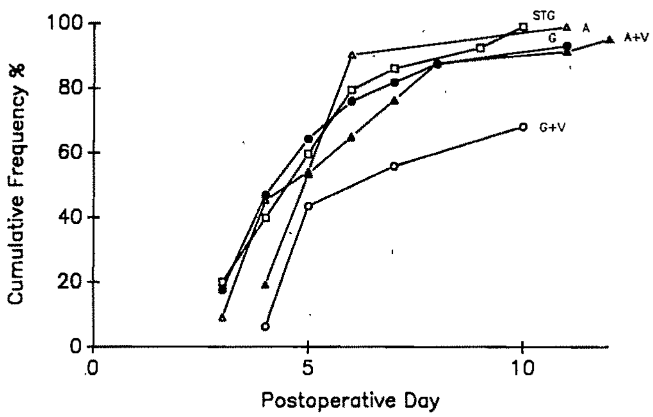

FIG. 1. Cumulative frequencies of postoperative day of starting adequate liquid oral intake after the various operative procedures. STG = subtotal gastrectomy. A = antrectomy. G = gastrojejunostomy. A + V = antrectomy with vagotomy. G + V = gastrojejunostomy with vagotomy.

of the day liquids or solids were started in patients with or without vagotomy.

Vagotomy

A comparison of all patients who had a vagotomy was made with all but one patient who did not have a vagotomy. This patient did not start adequate oral intake until the 65th day after a gastrojejunostomy and was excluded from this analysis. Liquid intake was started on the fifth postoperative day (5.3 ± 2.1, N = 42) when vagotomy was not done. This is in contrast to the ninth mean postoperative day (8.8 ± 7.4, N = 42) when vagotomy was done. This 3.5-day difference in means is significant ($p < 0.004$).

TABLE 4. *Cumulative Frequencies of Days Starting Solid Intake*

	Obstruction N = 24		No Obstruction N = 61	
Day	Cum %	Z Score*	Cum %	Z Score*
3			1.6	−0.76
4	8.3	−1.43	8.2	−0.67
5	12.5	−1.16	16.4	−0.58
6	20.8	−0.90	29.5	−0.49
7	29.2	−0.64	52.5	−0.41
8	50.0	−0.37	59.0	−0.32
9	66.7	−0.11	70.5	−0.23
10	70.8	0.15	73.8	−0.14
11	75.0	0.42	78.7	−0.05
12			80.3	0.04
13	83.3	0.94	82.0	0.13
14	87.5	1.21	83.6	0.22
15				
16	91.7	1.73		
17	100.0	2.00		
20			88.5	0.76
25			90.2	1.20
27			91.8	1.38
36			96.7	2.18
39			98.4	2.45
68			100.0	5.04

* Z score = SD below or above mean.

Analysis by operative procedure is shown in Figure 1, which compares the cumulative frequencies of the various operations up to the 12th postoperative day. There is no significant difference between patients who had gastrojejunostomy alone, antrectomy alone, antrectomy with vagotomy, and subtotal gastrectomy. However, there is a significant difference between these groups of patients and those who had vagotomy with gastrojejunostomy ($p < 0.01$).

Because of the sharp difference observed for the day of starting adequate liquid oral intake after vagotomy with gastrojejunostomy, this procedure was compared with vagotomy with pyloroplasty (Heineke-Mikulicz) done during the same period of review and meeting the criteria listed in Methods (Fig. 2). By the seventh postoperative day, 92% of the patients who had vagotomy with pyloroplasty were taking adequate liquids orally in contrast to 56% of the patients who had vagotomy with gastrojejunostomy ($p = 0.02$). This difference did not appear to be attributable to variations in suture technique or use of an electrosurgical unit. The mean time for the start of an adequate liquid intake for patients who had vagotomy with pyloroplasty did not significantly differ from the operative procedures (other than vagotomy with gastrojejunostomy) listed in Table 1.

Antecolic Versus *Retrocolic Anastomosis*

Most of the anastomoses (76%) were done in a retrocolic fashion. All but four of the gastrojejunostomies without vagotomy (76.5% = 13 patients), all but one of the gastrojejunostomies with vagotomy (93.8% = 15 patients), all but eight of the antrectomies with vagotomy (69.2% = 18 patients), all but three of the antrectomies without vagotomy (72.7% = 8 patients), and all but four of the subtotal gastrectomies (73.3% = 11 patients) were performed in a retrocolic fashion. No significant difference for the group as a whole was apparent in comparing antecolic to retrocolic anastomoses. Significant differences also were not apparent by nonparametric analyses of the individual operative procedures.

Nasogastric Tube

A nasogastric tube was used after operation in 81.2% of the patients. Analysis of a 24-hour nasogastric tube output for each of the first three postoperative days showed no correlation with the time of starting adequate oral intake of liquids or solids. Furthermore, there was no correlation between the total or average nasogastric tube output and day of starting adequate oral liquids or solids. The average output for all patients was 397 ± 34 ml (mean ± SE, N = 68) for the first postoperative 24 hours, 541 ± 66 ml (N = 68) for the second 24 hours, and 403 ± 58 ml for the third 24 hours (N = 58). There were some significant differences in mean nasogastric outputs when comparing the various operative procedures. The mean output during the first postoperative day for patients who had gastrojejunostomy alone was significantly greater ($p < 0.05$) than the other operations. In addition there were some random significant differences in mean 24-hour outputs among the operative procedures on the second and third postoperative days.

No Nasogastric Tube

Only 16 patients did not have a nasogastric tube during their postoperative course. Ten of these patients began adequate oral intake by the end of day 5. The remaining six patients began adequate oral intake by days 6 to 12.

Electrosurgical Unit

Only 34% of the patients had their gastroenterostomy stomas fashioned exclusively using an electrosurgical unit. This did not significantly affect the day of starting liquid or solid food.

Suture Versus *Staples*

Suture alone was used to construct the anastomosis in 96.5% of patients. Two layers of sutures were used in 65.9% of these patients. No significant difference was apparent between the use of a one- or two-layered anastomosis.

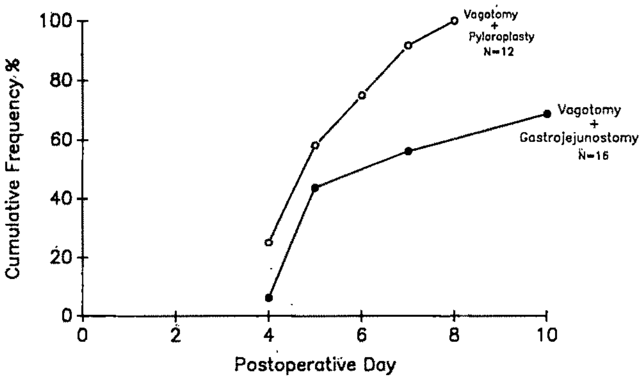

FIG. 2. Cumulative frequencies of postoperative day of starting adequate liquid oral intake after the vagotomy with gastrojejunostomy and vagotomy with pyloroplasty.

A valid comparison between sutures and staples cannot be made. Nevertheless, the three patients who had a stapled anastomosis began adequate liquids on days 4, 8, and 11 and solids on days 9, 11, and 14, respectively.

Surgeon

No analysis of individual surgeons was made because of the varible number of involved operative teams.

Reoperation

Eight patients had reoperation and were not included in any of the above analyses. Two reoperations were for small bowel obstruction occurring on postoperative days 18 and 35. Both patients were discharged from the hospital eating a regular diet before being readmitted for the obstruction. Three patients who had gastrojejunostomy alone had reoperation because of failure of gastric emptying on postoperative days 10, 14, and 28. Three patients who underwent antrectomy with vagotomy had reoperation because of failure of gastric emptying on postoperative days 10, 14, and 60. Upper gastrointestinal radiographs showed virtually no emptying in four patients and two showed minimal emptying. In all six of these patients, however, there was evidence of edema at the anastomosis. At reoperation, an instrument or finger passed through the anastomosis, indicating that it had not strictured to the point of closure, and no obvious technical errors from the original operation were evident. All patients undergoing reoperation consumed an adequate liquid diet by the eighth postoperative day (days 3, 4, 4, 5, 5, 8). Further analysis of the six patients who had reoperation because of failure of emptying was not carried out because of their small number and the arbitrary, variable criteria used for the timing of reoperation.

Discussion

The definition of delayed gastric emptying beginning in the immediate postoperative period of a gastrojejunostomy varies. It ranges from inability to tolerate oral intake by 48 hours,[2,3] or by 5 or 8 days[4–6] to 10 days after operation[7–9] or inability to tolerate solid food for more than 14 days after operation.[10] Others use the requirement of a nasogastric tube for more than 3[11] or 10[12] days after operation. Delayed emptying that persists for less than 3 weeks has been considered to be a milder form of the problem.[13] Few if any define what is meant by tolerating oral intake. The incidence of delayed gastric emptying after gastrojejunostomy also varies[1–3,5,11] because of the spectrum of definitions. Thus, the incidence ranges from 0 to 20%.[2,9,11]

The current study involves otherwise healthy patients and defines an adequate oral intake as that which is sufficient to prevent oliguria. Inability to do so constitutes a reasonable clinical definition of delayed gastric emptying when it is associated with nausea, vomiting, or a sensation of epigastric fullness that prevents further oral intake. The mean time by which all patients undergoing a gastrojejunal anastomosis with or without gastric resection or vagotomy can consume an adequate oral intake is 8 days. However, 84% of the patients could swallow an adequate liquid intake by this time. Only 8% of patients had sufficient oral intake of liquid by the third postoperative day, but this figure increased to 55% by the fifth day and to 91% by the eleventh day. Solid food was tolerated on the average 3 days after the start of an adequate oral liquid intake.

Multiple reasons have been proposed to explain why gastric emptying may be delayed after gastroenteric anastomoses. Several of the causes are either speculative or anecdotal. Explanations include edema, hematoma, anastomotic leak, ileus resulting from intra- or extra-abdominal infection, starch peritonitis, adhesions, potassium deficiency, pancreatitis, too small a stoma, inadvertent suture of anterior to posterior walls of anastomosis, too much inversion of tissue at the anastomosis, scarred (unsuitable) bowel used for anastomosis, mesocolic compression, retroanastomotic hernia, jejunogastric intussusception, marginal ulceration, kinking of the efferent loop, prolapse of mucosa through the anastomosis, nondependent anastomosis, malalignment of the anastomosis, and colonic distention compressing an antecolic gastrojejunostomy. Other proposed causes include chronic preoperative obstruction, inanition, gastritis, a blind loop, too large an anastomosis, food bolus impaction, two-layer as opposed to one-layer anastomosis, an improperly placed stoma, too long or too short a jejunal loop, narcotic medication, the efferent loop situated higher than the afferent loop, the direction of peristalsis in the efferent loop not corresponding to normal direction of emptying by the stomach, autonomic nerve dysfunction or gastric atony, and experience of the surgeon.[3,6,11,14,15] About the only technical issue that there appears to be some agreement on is the lack of apparent relationship between delayed emptying and an antecolic or a retrocolic gastrojejunal anastomosis.[4] [16]

Often no predisposing factors are identified[1] and the cause of postoperative gastric retention frequently is not found at reoperation. This suggests that many of the anatomic and some of the functional causes are preventable. Thus, it appears that transient functional and/or anatomic changes account for delayed emptying in the majority of instances. The observation that most patients progress to an adequate oral intake with conservative management support these interpretations.

Edematous swelling is probably the most common cause of early postoperative stenosis of the stoma.[17] In contrast, others have reasoned that mechanical causes should produce obstruction equally as often in the afferent stomal inlet as in the efferent outlet; however, afferent inlet dysfunction is unusual.[18] However, afferent limb peristalsis might overcome any edema at the anastomotic site. Such edema most often is not related to plasma colloidal oncotic pressure. No relationship was found in one study between delayed gastric emptying and postoperative serum protein values or colloidal osmotic pressure.[19] Although extreme forms of hypoproteinemia may be associated with anastomotic edema, such hypoproteinemia is rarely seen in patients undergoing operation. Use of an electrosurgical unit to divide the stomach and jejunum might be expected to cause greater edema, but our data do not support the contention that such a unit contributes to delayed emptying. What is interpreted as anastomotic edema is seen on virtually every upper gastrointestinal radiograph obtained in the immediate postoperative period. However, it is difficult to correlate the degree of apparent edema with delayed emptying of radiographic contrast material.

It is also difficult to distinguish by radiography between anastomotic edema and submucosal hemorrhage. Submucosal hemorrhage at the site of anastomosis can contribute to stomal obstruction, but there are no substantive data indicating how long a hematoma contributes to the problem. The opinion has been expressed that submucosal hemorrhage at the site of the anastomosis usually subsides within 10 days.[20] In contrast, obstruction from a spontaneous hematoma of the jejunum in a patient receiving warfarin is known to usually subside within 48–72 hours.[21] Experimentally, however, anastomotic hematoma or edema generally subsides by the 29th postoperative day.[22]

Few, if any, would argue that gentle handling of tissue is essential to minimize the degree of anastomotic edema. While roughness contributes, delayed gastric emptying frequently cannot be explained on the basis of trauma alone. No matter how gently the stomach is handled, a problem with emptying may still occur[23] in the absence of an obvious technical error. Delicate partition alone of the bowel can result in edema, as is often seen after division of a transverse colostomy.

Some believe that atony of the gastric remnant as a result of vagotomy is a common cause of delayed emptying. This explanation is based on the frequent observation that radiographic contrast or an endoscope or, at reoperation, an instrument or finger can be passed through the anastomosis. Although these maneuvers may be reassuring that no gross technical error was made to account for delayed emptying, they do not help to quantitate the degree of resistance (for example, from edema) offered by the anastomosis. Gastric atony has even been invoked as a cause of efferent stomal dysfunction in patients who have subtotal gastrectomy *without vagotomy.*[18] Others, however, believe that atony of the gastric remnant is rare.[24] The notion of atony associated with vagotomy is not in keeping with a currently accepted physiologic concept that parasympathetic denervation of the fundus and antrum cause a loss of receptive relaxation of the stomach and thus faster emptying of liquid. Furthermore, postoperative gastric atony may be euphemistic, as an atonic stomach with a patent outlet should empty by gravity. If this is the case, even "mild" anastomotic edema may play an important role in delayed emptying. The concept of atony also does not account for the fact that a prolonged period of delayed emptying is frequently overcome by redoing the gastroenteric anastomosis in this circumstance. On the other hand, impaired tone of the residual gastric pouch has been described after gastrectomy with vagotomy beyond the immediate postoperative period,[25] but the prevalence and significance of this finding is still unclear.

One study suggests that gastric tone, jejunal peristalsis, changes in intra-abdominal pressure, diaphragmatic motion, and gravity are probably the primary factors in emptying the gastric remnant.[26] Gastric evacuation requires a pressure gradient from stomach to intestine, but the significance of gravity or respiratory movements has been questioned.[27] However, prolonged gastric emptying of barium (at least twice as long) was observed in the head down compared to the upright position in 80% of patients after subtotal gastrectomy without vagotomy.[26] It is not difficult to imagine that in the presence of a certain degree of anastomotic edema, the pressure gradient might be insufficient for drainage to occur by gravity.

No significant differences were observed in the current study for the time it took patients to consume an adequate oral liquid intake after gastrojejunostomy or subtotal gastrectomy without vagotomy or vagotomy with antrectomy. In contrast, it took significantly longer for patients who underwent vagotomy with gastrojejunostomy to consume an adequate oral intake; this was particularly noticeable after the fifth postoperative day (Fig. 1). At least 77% of the former group of patients consumed an adequate intake by the seventh postoperative day, which is in contrast to 56% of the patients who had a gastrojejunostomy with vagotomy. This observation could be due either to a speculative perturbation resulting from vagotomy or a type II statistical error, which is also a problem with other studies reporting some or no differences between various types of operations.[2,9,12,13,28] These studies are difficult to compare because of the lack of reasonably precise definitions of adequacy of oral intake and variable technical, operative details.

The current data suggest that vagotomy *per se* does not account for the apparent delay in consumption of an adequate oral liquid intake. If vagotomy alone were important, one would expect delayed emptying also to occur after vagotomy with pyloroplasty and vagotomy with antrectomy. This was not observed in the current study. Similar reasoning also suggests that gastroenterostomy alone also does not account for delayed emptying. Motor incoördination of the efferent loop might increase resistance to gastric outflow,[29] but the prevalence and significance of this possibility in the immediate postoperative period is unclear.

Some believe that longstanding gastric outlet obstruction is a predisposing cause of delayed gastric emptying.[6,30] The usual explanation is that obstruction leads to a loss of gastric tone. It has been suggested that subtotal gastrectomy is associated with a lower incidence of delayed gastric emptying than vagotomy with drainage done for obstructing ulcer disease.[7] The current study suggests that gastroenterostomy with or without vagotomy is not associated with prolonged emptying in the presence of obstruction. Vagotomy with gastroenterostomy is a very satisfactory long-term procedure for obstruction.[31,32]

Whatever the causes of delayed emptying may be, it is difficult to distinguish the basis of obstruction by radiographic[8] and/or endoscopic means. Some degree of anastomotic narrowing was seen in all of our patients who had gastrointestinal radiographs in the immediate postoperative period. Anastomotic edema is also observed after low anterior resection of the rectum,[33] but clinically significant "outlet obstruction" is unusual following this procedure. However, an important difference between intestinal and gastroenteric anastomoses is that the former have different proximal peristaltic properties than the residual stomach anastomosed to the proximal jejunum.

The number of confounding variables involved in a patient's ability to consume an adequate oral intake of liquids or solids after operation makes it exceedingly difficult to identify those aspects that are significant. This is further compounded by the observations that gastric emptying judged to be normal or abnormal by barium flowing through a gastrojejunal anastomosis or more objective studies such as kinetic analyses of isotopic rates of gastric emptying do not necessarily correlate with adequacy of postoperative oral intake and maintenance of normal hydration or even nutrition.

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Once cefoxitin was the only single agent you had for prophylaxis and treatment of mixed abdominal and pelvic infections. Now it's being steadily replaced in hospitals by something better...CEFOTAN. Here's why.

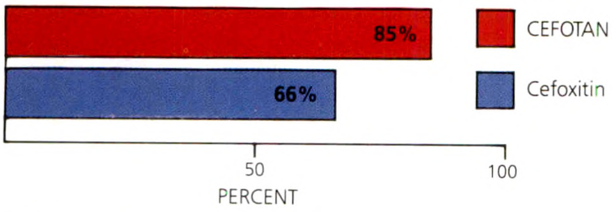
Superior activity.

CEFOTAN is 8 to 16 times more active than cefoxitin against the most commonly isolated gram-negative aerobes—*Escherichia coli, Klebsiella pneumoniae,* and *Proteus mirabilis.**[1] What's more, CEFOTAN possesses activity against *Enterobacter* sp[2]...often resistant to cefoxitin.

CEFOTAN is also as active as cefoxitin against *Bacteroides fragilis.**[3-6] Recent studies involving 8 US medical centers, however, found more *B fragilis* isolates susceptible to CEFOTAN than to cefoxitin.[7]

*In vitro activity does not necessarily correlate with in vivo effectiveness.

Susceptibility† of *B fragilis,* CEFOTAN vs cefoxitin[7]



†FDA-recommended susceptible MIC breakpoints for both are $\leq 16\ \mu g/mL$.

Longer duration of action... more convenient dosing.

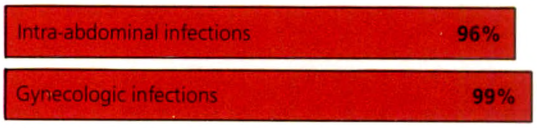
In comparative studies CEFOTAN provided antimicrobial activity against susceptible pathogens for a full 12 hours, while cefoxitin provided coverage for less than 6 hours.[8-9] As a result, only a single dose of CEFOTAN is required for surgical prophylaxis, compared with the three-dose regimen of cefoxitin—improving patient comfort and reducing hospital costs.

Please see next page for brief summary of prescribing information.

Exceptional clinical success rates.

The twice-daily therapeutic dose of CEFOTAN demonstrated excellent clinical success rates,‡ as you can see below.

Clinical success rates‡[10]



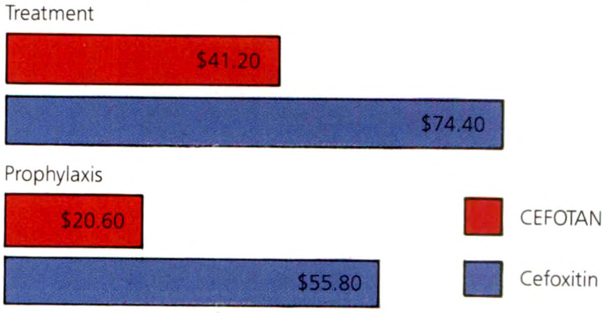
‡Clinical success is defined as complete clearing or substantial improvement in signs and symptoms of infection.

CEFOTAN is indicated for the treatment of intra-abdominal and gynecologic infections due to susceptible pathogens including *Bacteroides* species such as *B fragilis, B bivius,* and *B disiens,* but not *B distasonis, B ovatus,* or *B thetaiotaomicron.*

Cost savings without compromise.

Treatment with CEFOTAN can save your hospital 45% in total costs for therapy when compared with cefoxitin, and 63% for surgical prophylaxis. Furthermore, CEFOTAN is well tolerated, with the safety profile you've come to expect from cephalosporins.[10]

Cost per day,§ CEFOTAN vs cefoxitin



§Based on overall antibiotic acquisition, preparation, and delivery[11] costs for comparable regimens: Treatment—CEFOTAN, 2 g × 2; cefoxitin,[12] 2 g × 4. Prophylaxis—CEFOTAN, 2 g × 1; cefoxitin,[12] 2 g × 3.

In intra-abdominal and gynecologic infection due to indicated organisms

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For Intravenous or Intramuscular Use
BRIEF SUMMARY

INDICATIONS AND USAGE

TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary tract infections caused by *E coli, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris, Providencia rettgeri*, and *Morganella morganii*).

Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.

Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.

Gynecologic infections caused by *Staphylococcus aureus*† (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus* species (excluding enterococci), *E coli, Proteus mirabilis, Neisseria gonorrhoeae, Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*), *Fusobacterium* species,† and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species†).

Intra-abdominal infections caused by *E coli, Klebsiella* species (including *K pneumoniae*†), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*).

Bone and joint infections caused by *Staphylococcus aureus*.†

***NOTE:** Some strains of *Staphylococcus epidermidis* are resistant to cefotetan.

† Efficacy for this organism in this organ system was studied in fewer than ten infections.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.

PRECAUTIONS

GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state. Prothrombin times should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels of Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approx 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approx 2-4 times the usual human dose), only 1 of 10 treated animals was affected, and the degree of degeneration was mild. Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired

CEFOTAN® (cefotetan disodium)

fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In clinical studies the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5 percent of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4 percent of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2 percent of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2 percent of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than one percent of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

DOSAGE AND ADMINISTRATION

TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dose*	Every 12 hours
10-30	Usual Recommended Dose*	Every 24 hours
<10	Usual Recommended Dose*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED

CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21)

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Orthotopic Liver Transplantation for Primary Sclerosing Cholangitis

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The incidence or diagnostic rate of sclerosing cholangitis is increasing. Because of the lack of effective medical or surgical therapy for patients with end-stage liver disease and sclerosing cholangitis, results with orthotopic liver transplantation were examined. The results of 55 consecutive liver replacements for this disease were reviewed. The 1- and 2-year actuarial survival rates are 71% and 57%, respectively. Orthotopic liver transplantation for end-stage liver disease from sclerosing cholangitis has emerged as the most effective therapy.

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SCLEROSING CHOLANGITIS is an enigmatic disease usually found in men younger than 50 years and, more often than not, is associated with inflammatory bowel disease, particularly ulcerative colitis. The treatment modalities used for this disease have been as varied as the descriptions of the disease itself and illustrate the dissatisfaction with the currently available medical/surgical therapies. Although the histologic course of sclerosing cholangitis is considered benign, the disease most often takes an indolently malignant course and is, in fact, a pernicious disease. Importantly, there is an apparent increasing incidence, or at least an increasing diagnostic rate, of the disease in most developed countries.

We report our experience with hepatic replacement in 55 patients who had primary sclerosing cholangitis as the indication for liver transplantation. We have tried (1) to determine the applicability, success rate, and survival of orthotopic liver transplantation for patients with primary sclerosing cholangitis, (2) to determine the recurrence rate of sclerosing cholangitis, should it occur, and (3) to assess the course of the associated inflammatory bowel disease under immunosuppression after liver transplantation.

Case Material and Methods

Between January 1, 1980, and June 30, 1986, 604 primary orthotopic liver transplants were performed at the University of Colorado Health Science Center (through 1980), the University Health Center of Pittsburgh (since 1981), and the Pittsburgh-affiliated Baylor University Medical Center at Dallas (since 1985). All patients were treated with combination prednisone–cyclosporine therapy as has been described elsewhere.[1-3] Patients were considered to have "primary" sclerosing cholangitis[4-7] when there were (1) typical cholangiographic findings of the disease, (2) pathologic confirmation of the disease from the total hepatectomy specimen, and (3) the absence of a history or pathologic evidence consistent with secondary biliary cirrhosis from other causes.

Fifty-five patients received orthotopic liver transplantation for end-stage primary sclerosing cholangitis. Thirty-five were male (63.6%) and twenty were female (36.4%). Their ages ranged from 15 to 58 years with a median age of 36 years. Only four patients were older than 50 years.

The indications for transplantation were persistent or recurrent variceal bleeding in 27.2% (15 of 55 patients),

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TABLE 1. *Biliary and Intestinal Operations before Orthotopic Liver Transplantation*

	No. of Patients
Hepaticojejunostomy	15
Cholecystectomy	6
T-tube drainage of the choledochus	5
Cholecystectomy and percutaneous choledochal drainage	3
Choledochoduodenostomy	1
Cholecystojejunostomy	1
Distal splenorenal shunts without prior biliary tract surgery	2
Partial or total abdominal colectomy	4
Proctocolectomy with ileostomy	3
Small bowel resection (Crohn's disease)	1

ascending cholangitis in 27.2% (15 of 55 patients), or hepatic decompensation, including encephalopathy, coagulopathy, anorexia, ascites, fatigue, pruritus, and/or 3–4+ varices, in 45.5% (25 of 55 patients). Because of the risk of cholangiocarcinoma, the timing of transplantation cannot be accurately defined. In general, however, transplantation is encouraged when the bilirubin level exceeds 10 mg/dl or is rapidly rising, when the patient's lifestyle has begun to significantly deteriorate, or with any suspicion of cholangiocarcinoma.

Thirty-six (65.4%) of 55 patients had a history of inflammatory bowel disease. Thirty-two patients had ulcerative colitis, and four patients had Crohn's disease. Cholangiocarcinoma was found in the hepatectomy specimen of five patients (9%). Three of 55 patients had had a carcinoma of the right colon removed by radical right colectomy, 11, 4, and 4 years, respectively, before liver transplantation without evidence of recurrence.

Thirty-one (56.3%) of 55 patients had undergone prior biliary tract surgery for diagnosis or treatment of the sclerosing cholangitis (Table 1). Fifteen patients had undergone hepaticojejunostomy, six had cholecystectomy alone, five had T-tube drainage of the choledochus, three had cholecystectomy and percutaneous choledochal drainage, one had choledochoduodenostomy, and one had cholecystojejunostomy.

Eight patients (14.5%) had undergone prior bowel surgery for either inflammatory bowel disease or for complicating carcinoma. Three patients had undergone partial or total abdominal colectomy. Two of the three patients had proctocolectomy with ileostomy, and one patient had proctocolectomy with an ileoanal pullthrough. A fourth patient had undergone a small bowel resection for Crohn's disease.

The liver disease was diagnosed 1–16 years (mean: 5.8 years) before transplantation, and the bowel disease, when present, had existed from 2 to 29 years (mean: 14.8 years). In all but five of the 36 cases with coexisting inflammatory bowel disease, the bowel disease preceded the sclerosing cholangitis.

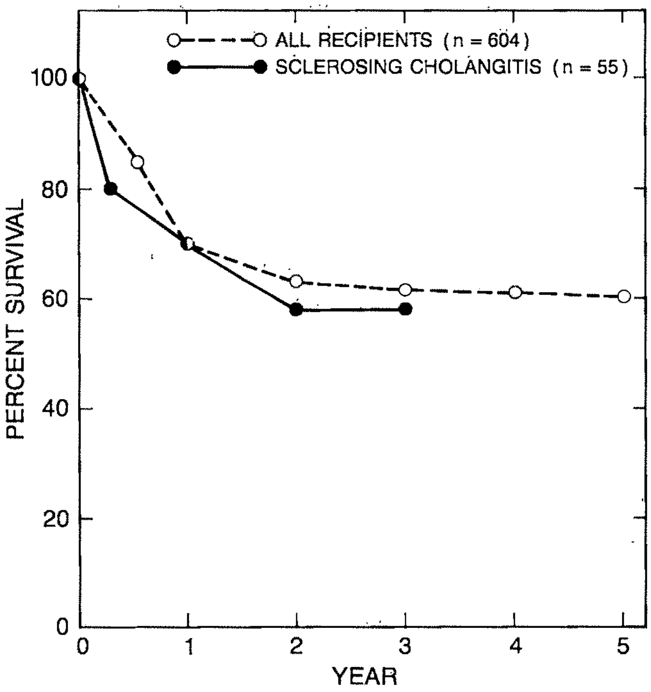


FIG. 1. Actuarial survival after orthotopic liver transplantation.

Results

Survival

As of September 1, 1986, there were 37 patients living (67%) and 18 dead (33%) with a mean follow-up period of 19 months (range: 4–46 months). The actuarial survival rates at 3, 6, 9, 12, 24, and 36 months were 80%, 76%, 76%, 71%, 57%, and 57%, respectively, calculated by the life table analysis of Kaplan-Meier. (Fig. 1). The longest surviving patient who had transplantation for primary sclerosing cholangitis has been observed for 46 months.

Cause of Death

Eleven patients died within 3 months of transplantation, all from direct complications of transplantation or the associated immunosuppression. Technical failures, primary nonfunction of the graft, infectious complications, and irreversible acute rejection were the leading causes of death. Two patients died between 3 and 6 months, one of graft failure and sepsis, and another of biliary sepsis due to recurrence of cholangiocarcinoma. Between 6 and 12 months one patient died of an unrecognized lymphoproliferative disorder. Three patients

TABLE 2. *Causes of Death after Orthotopic Liver Transplantation*

Time of Death after Transplant	No. of Deaths	Cause of Death	
0–3 months	11 patients (19 transplants)	Nine deaths related directly to graft failure: cause of graft failure (including retransplantation)	
		primary nonfunction	7
		technical failure	3
		acute rejection	4
		Two deaths related to immunosupression	
		intra-abdominal abscess	1
		cryptococcal meningitis	1
3–6 months	1 patient	Graft failure and sepsis	
	1 patient	Biliary sepsis and recurrent cholangiocarcinoma	
6–12 months	1 patient	Unrecognized lymphoproliferative disorder	
1–2 years	1 patient	Recurrent cholangiocarcinoma	
	1 patient	Systemic fungal infection	
	1 patient	GI bleeding and liver failure from portal vein thrombosis	
2–3 years	No deaths		
>3 years	1 patient	Chronic rejection	

died between 1 and 2 years, one of recurrent cholangiocarcinoma, one of systemic fungal infection, and the other of gastrointestinal bleeding and liver failure due to rethrombosis of the portal and superior mesenteric veins which had been opened with thrombophlebectomy at the time of transplantation. No patient died between 2 and 3 years after transplantation. One patient died of liver failure due to chronic rejection more than 3 years after transplantation (Table 2).

Unrecognized Cholangiocarcinoma

Previously unrecognized cholangiocarcinoma was found in the surgical specimen of five of the 55 patients. There were three women and two men with an average age of 35.4 years (range: 24–37 years). Two patients had no history of inflammatory bowel disease; three had had ulcerative colitis for 16, 20, and 29 years. The patient who had had ulcerative colitis for 16 years had undergone a right colectomy 4 years before liver transplantation for a Duke's B carcinoma of the colon with no evidence of recurrence. The clinically evident liver disease in this subset of patients had been present 1, 2, 4, 7, and 14 years, clearly illustrating that longstanding liver disease is not a prerequisite for the development of cholangiocarcinoma. Two of these patients died as a result of recurrent cholangiocarcinoma 4 and 12 months after transplantation. Three patients are alive, but the follow-up period is short. The first patient still living is 1 year post-transplantation, received adjunctive chemotherapy and radiotherapy, but has recurrence of disease. The remaining two patients are 3 months post-transplant without evidence of recurrence: both have undergone radiotherapy and one will undergo chemotherapy as well.

Inflammatory Bowel Disease after Liver Transplantation

During the observation period of 4 months to 4 years, nine (34.5%) of 26 patients who had had inflammatory bowel disease before transplantation and who survived more than 3 months after transplantation developed reactivation or exacerbation of the bowel disease. However, the recurrent inflammatory bowel disease was minimally symptomatic in seven of the nine patients, requiring only short-term treatment with sulfasalazine, and was moderate in two of nine patients, requiring long-term sulfasalazine therapy and increased doses of steroids.

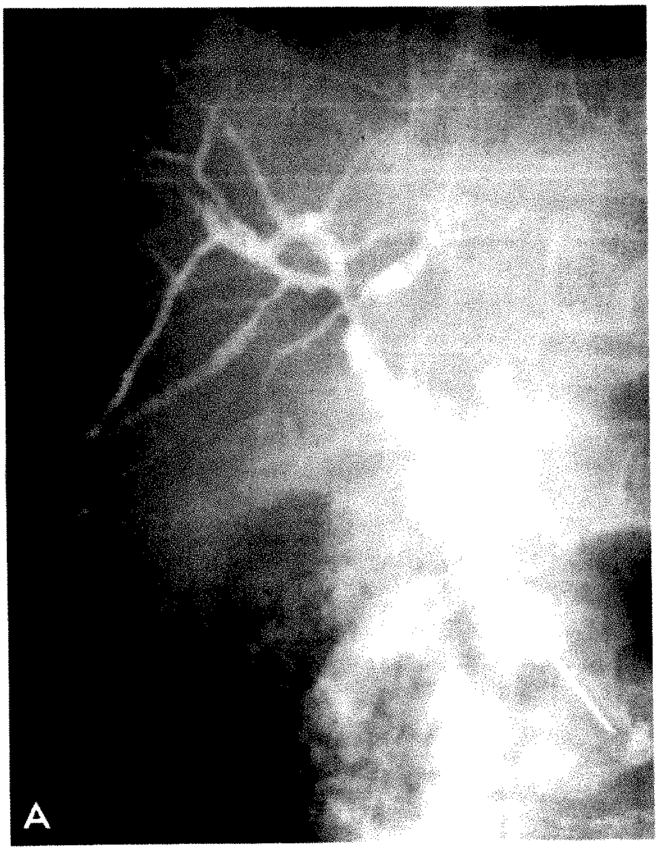
Annual or semiannual colonoscopic examinations of the surviving patients have not detected any colorectal malignancy during this relatively short period of observation, but in none of the patients with pre-existing abnormalities have the colonoscopic findings become totally normal. It is also noteworthy that none of the patients without a pre-existing history of inflammatory bowel disease has developed it after transplantation.

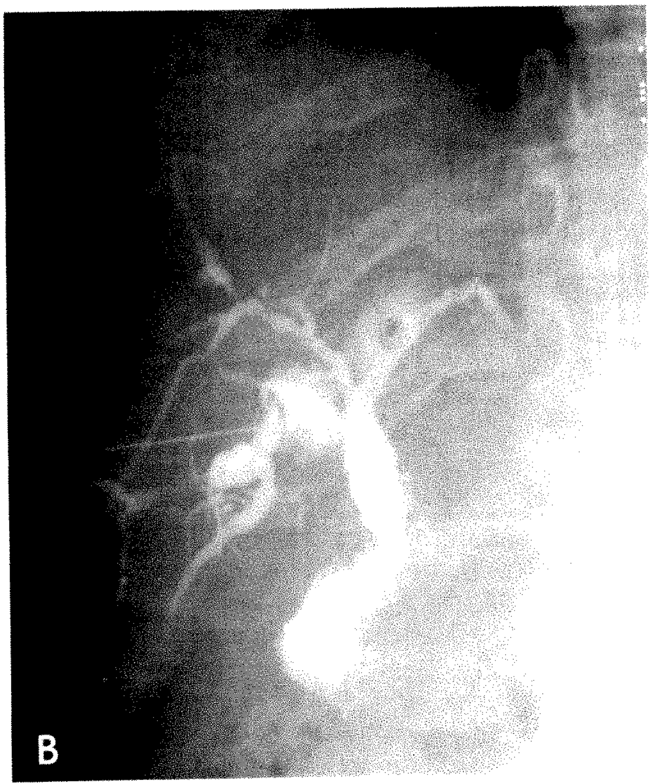
Recurrence of Sclerosing Cholangitis

In one patient, chemical and radiological abnormalities developed in the graft compatible with sclerosing cholangitis 1 year after transplantation (Fig. 2A), but the abnormalities have been stable for the ensuing year. Four patients whose original liver disease was not sclerosing cholangitis also had similar abnormalities develop after histologically proven graft rejection (Fig. 2B).

Discussion

Primary sclerosing cholangitis remains a disease of unknown cause. It has become the third most common





FIGS. 2A and B. *A*. Cholangiogram showing changes of sclerosing cholangitis 1 year after transplantation. The original diagnosis was sclerosing cholangitis. *B*. Cholangiogram showing changes of sclerosing cholangitis in a patient with a >90% stenosis of the hepatic artery and after multiple biopsy-proven rejections. The original diagnosis was chronic active non-A, non-B hepatitis.

indication for orthotopic liver transplantation in adults, the first being postnecrotic cirrhosis and the second being primary biliary cirrhosis. Treatment has been attempted with steroids, cholestyramine, azathioprine, D-penicillamine,[8] choledochoenteric anastomoses,[9] and choledochal drainage by T-tube or Silastic® transhepatic stents.[10]

Wiesner and LaRusso,[11] have reported the largest group of patients with primary sclerosing cholangitis treated without transplantation at a single institution. Thirty-nine (78%) of their 50 patients had adequate follow-up for presentation. Thirteen (33%) of the 39 patients were dead after a mean interval of 57 months after diagnosis. At the time of reporting, 26 patients (66%) were alive, but 12 had end-stage liver disease. Thus, an unsatisfactory result had been obtained in at least 64% of the cases.

Cameron et al.,[10] have reported the operative placement of Silastic transhepatic stents in a group of 11 patients. Eleven of the original 22 patients were not selected for operation, and of those operated on the majority have either died or come to transplantation, including three patients treated by us. The prior performance of this type of operation has made transplantation exceptionally difficult.

The fact that a satisfactory result could be obtained in two thirds of the 55 patients herein reported after a mean follow-up of more than 1.5 years is encouraging. All patients were medical/surgical treatment failures with liver disease that preceded the transplantation by a mean of 68 months. Even though 14 patients died in less than 1 year, the 71% actuarial 1-year survival and the 57% 2-year survival rates are not significantly different than that of the overall group of 604 patients of our total series.

Cholangiocarcinoma was found at pathologic examination of the removed liver specimen in five (9.9%) of 55 patients. Two of these recipients have died and one has recurrence of disease. Although two patients are still disease free, their long-term outlook remains to be determined since the follow-up period has been short. We currently believe that any patient undergoing stenting of the biliary tree should have brushings, cytologic examination, and/or needle biopsies obtained in an attempt to bring these patients to earlier transplantation before malignant changes occur.

This experience demonstrates the effectiveness of orthotopic liver transplantation for patients with advanced primary sclerosing cholangitis. In the future, liver replacement should not be reserved as a last minute operation for moribund patients who have undergone the gamut of palliative medical and surgical therapies that have not been shown to be effective in prolonging life or reducing morbidity. Specifically, palliative operations such as choledochoenterostomy for sclerosing cholangitis should be avoided since the same results can be obtained by transhepatic biliary drainage and balloon dilatation or by endoscopic procedures, particularly in those patients whose sclerosing cholangitis is limited to a narrow segment of the extrahepatic biliary tree. With a 2-year survival rate of 57%, orthotopic liver transplantation has emerged as the sole form of therapy that offers patients who had failed treatment a chance at returning to normalcy at the cost of the least number of lives.

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Partial Biliary Obstruction Caused by Chronic Pancreatitis

An Appraisal of Indications for Surgical Biliary Drainage

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This paper presents a retrospective review of 38 patients with intrapancreatic bile duct strictures secondary to chronic alcoholic pancreatitis. The strictures were identified by endoscopic retrograde cholangiopancreatography (ERCP). All patients with pancreatic cancer and gallstone pancreatitis were excluded. The mean alkaline phosphatase and total bilirubin values were 344 ± 57 IU/dl and 4.4 ± 0.7 mg/dl, respectively. The mean stricture length was 3.9 ± 0.5 cm, and the mean common bile duct (CBD) diameter was 1.8 ± 0.2 cm. The degree of bilirubin and alkaline phosphatase elevation did not correlate with stricture length or the severity of bile duct dilatation. Eighteen of the 38 patients received surgical biliary drainage (BD) as part of their initial therapy, and 20 patients did not. Liver function tests, intrapancreatic stricture length, and the degree of proximal CBD dilation were comparable in these two groups. Patients not undergoing BD did well clinically as only one patient required BD over an average follow-up period of 3.8 years. In conclusion, bypass of these strictures is usually unnecessary, and most patients may be safely treated without operation.

INTRAPANCREATIC BILIARY STRICTURES have been estimated to occur in from 3 to 29% of patients with chronic alcoholic pancreatitis.[1-3] Opinions regarding the clinical significance and appropriate treatment for these lesions are variable. Strictures are often suspected in patients with clinical and laboratory signs of biliary stasis in conjunction with an acute exacerbation of chronic pancreatitis. Operative biliary drainage has often been recommended to prevent both the acute development of cholangitis and late development of biliary cirrhosis.[4,5] The low incidence of cholangitis and biliary cirrhosis in association with biliary strictures has prompted others to advocate a less aggressive approach to the care of these patients.[3,6-8] Since all prior published reports of patients with biliary strictures due to benign pancreatic disease report results of operative therapy, little is known about the natural history of patients who are not operated on. This study summarizes the clinical course of 38 patients with biliary strictures and chronic pancreatitis in an attempt to compare the risks and benefits of nonoperative therapy (20 patients) with those of traditional operative drainage of the biliary tree (18 patients).

Patients and Methods

Endoscopic retrograde cholangiopancreatography (ERCP) records from the Minneapolis Veterans Administration Hospital were reviewed from 1973 to 1985. All patients with clinical and radiologic evidence of chronic pancreatitis who were found to have an ERCP-proven stricture of their intrapancreatic common bile duct (CBD) were included in this study. Inpatient and outpatient medical records of each patient were reviewed. The ERCPs were interpreted by a single staff radiologist (H.A.). Patients with either choledocholithiasis or pancreatic cancer as the possible cause of ductal abnormalities were excluded.

All results are presented as mean ± SEM. Student's t-test and correlation coefficients were used for statistical comparison. A p value <0.05 was considered significant.[9]

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Results

Clinical Features

The mean age of the 38 patients was 49.5 years with a range from 23 to 66 years. Thirty-seven of the 38 patients were men. All patients had a long history of alcohol abuse, with over 60% having had one or more previous episodes of acute pancreatitis. The presenting signs and symptoms were abdominal pain (92%), weight loss (34%), jaundice (29%), nausea (24%), emesis (16%), fatigue (11%), gastrointestinal bleeding (8%), anorexia, fever, and ascites (3%).

Laboratory Values

The serum alkaline phosphatase was the laboratory test most frequently elevated at the time of admission (63% of patients) with an average value of 344 ± 57 IU/dl (normal range: 21–91 IU/dl). The total serum bilirubin level was elevated in 50% of patients, with an average value of 4.4 ± 0.7 mg% (normal range: 0.3–1.0 mg%). The SGOT was elevated in 54% of patients.

ERCP Findings

The intrapancreatic portion of the common bile duct (CBD) was strictured on ERCP in all patients. The mean length of the strictures was 3.9 ± 0.5 cm. The CBD proximal to the stricture was dilated in 64% of patients, with an average duct diameter of 1.8 ± 0.2 cm (normal diameter <1.0 cm), and a range from less than 1.0 to 4.0 cm. The configuration of the CBD was variable, as seen in Figures 1–4. The pancreatic ductal system routinely revealed a wide range of changes consistent with chronic pancreatitis. Findings varied from early side branch blunting to dilatation, tortuosity, and segmental stenosis of the main pancreatic duct. Pseudocysts were demonstrated in the pancreas in 18 of 38 patients (47%).

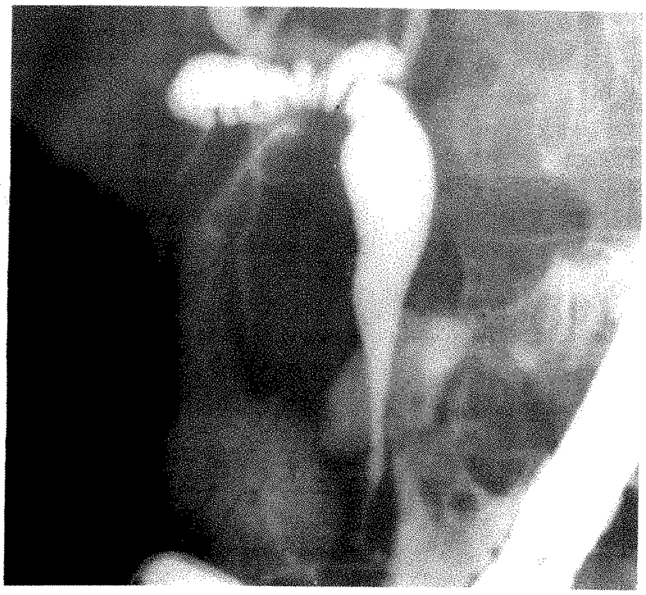

FIG. 1. A 48-year-old white man had pain and jaundice. Admission laboratory values were alkaline phosphatase of 750 IU/L and total bilirubin of 8.1 mg/dl. A 7.0-cm biliary stricture with a 1.4-cm diameter proximal CBD is seen on this cholangiogram. This patient was treated successfully with conservative medical therapy.

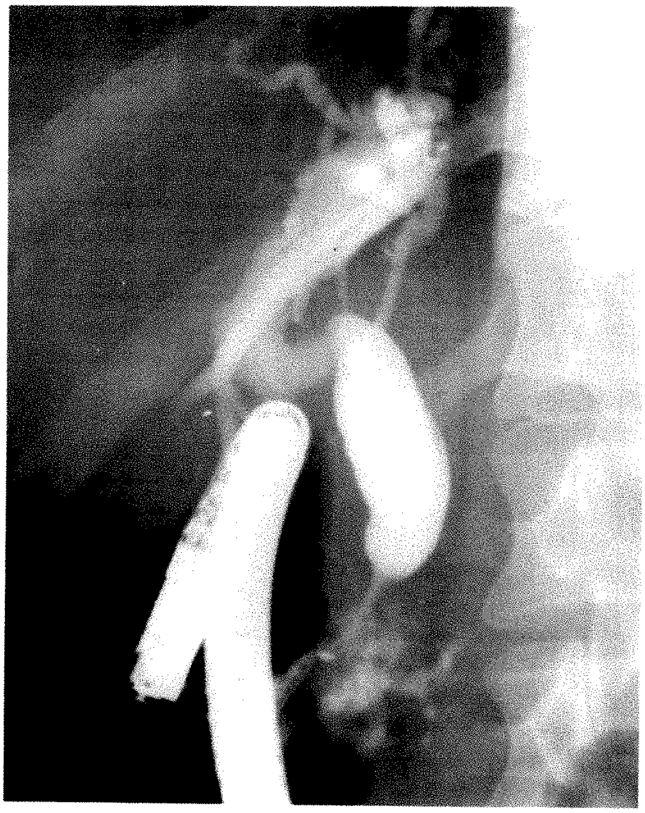

FIG. 2. A 36-year-old white man had recurrent pain and jaundice. Admission alkaline phosphatase level was 395 IU/L and total bilirubin level was 10.0 mg/dl. A 2.8-cm biliary stricture with 1.3-cm diameter proximal CBD was seen on this cholangiogram. This stricture was treated by choledochoduodenostomy. Follow-up for 1 year revealed no further problems.

Therapy

The various treatments the 38 patients received are depicted in Figure 5. In 18 patients, surgical biliary drainage (BD) was part of the initial therapy, whereas the remaining 20 patients did not have BD. Of the 18 patients who had BD, 13 had a bilioenteric anastomosis, and five had T-tube drainage of the common bile duct. Of the 20 patients who did not have BD, 15 had other surgical procedures performed, and five were treated strictly with nonsurgical measures. Concomitant pan-

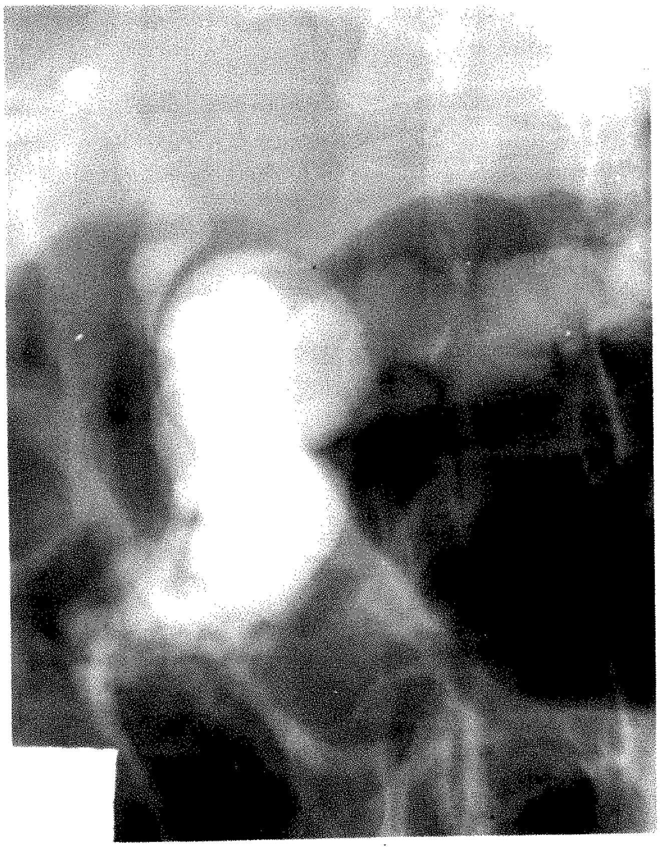

FIG. 3. A 54-year-old white man had weight loss and fatigue. His admission liver function tests were normal. ERCP revealed an intrapancreatic CBD stricture with no proximal CBD dilation. A pseudocyst was seen in the head of the pancreas displacing the CBD. Treatment consisted of a Roux-Y pancreaticojejunostomy (Puestow). Eight-year follow-up revealed no further biliary or pancreatic problems.

creatic procedures were performed in 23 of 38 patients, and consisted of pseudocyst drainage in 13, longitudinal pancreaticojejunostomy in nine (Puestow procedure), and pancreatic biopsy in one patient.

There were four treatment failures as defined by the need for a subsequent biliary procedure. Three occurred in the 18 patients initially undergoing drainage, and one occurred in the patients who did not have BD. One patient required conversion of a cholecystojejunostomy to a choledochojejunostomy subsequent to a severe episode of acute cholangitis, and two patients required choledochoduodenostomies after prolonged T-tube drainage. One patient in the group that did not have BD who experienced a treatment failure returned 4 years after conservative therapy with clinical sepsis, and underwent cholecystectomy, CBDE, and T-tube drainage of the common duct. However, his preoperative sepsis was found at operation to be due to an infected pancreatic pseudocyst, rather than CBD disease. All four of these patients who had treatment failure subsequently did well.

Postoperative Complications

There were no in-hospital deaths. Five major postoperative complications occurred including two subphrenic abscesses, both occurring after Puestow pancreaticojejunostomies; an anastomotic leak that occurred after a Puestow procedure; a peripancreatic abscess after a pancreatic pseudocystogastrostomy and cholecystectomy; and one severe episode of pneumonia.

Liver Histopathology

Intraoperative liver biopsies were obtained in 24 patients (Table 1). Three of 24 biopsy specimens revealed biliary cirrhosis (12%).

Comparison of Patients Who Had BD Versus *No BD*

Table 2 summarizes laboratory and clinical data for patients receiving BD as part of their initial therapy compared with those who did not. Although the mean serum bilirubin and alkaline phosphatase levels were higher in the group undergoing BD, the differences were not statistically significant. The biliary stricture lengths and CBD diameters proximal to the strictured area were nearly identical. The average length of follow-up was also comparable between groups.

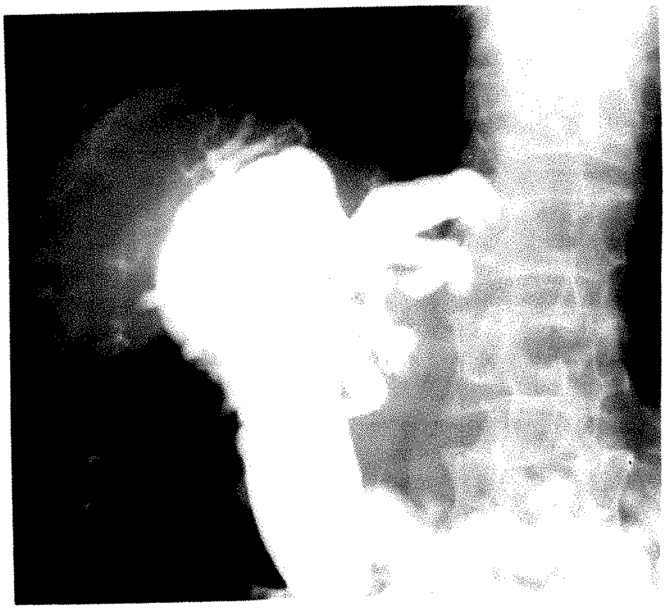

FIG. 4. A 53-year-old white man had abdominal pain. His admission liver function tests were normal. ERCP revealed a 3.0-cm intrapancreatic CBD stricture with a proximal CBD dilated to 4.0 cm. Treatment consisted of a Puestow pancreaticojejunostomy and choledochoduodenostomy. No further problems developed during 26 months of follow-up.

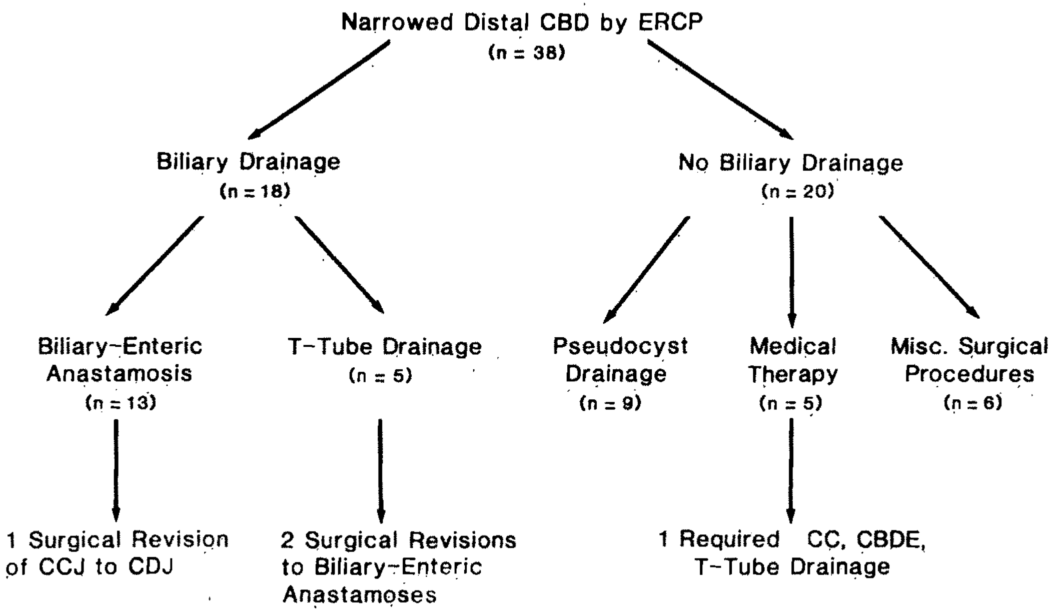
Narrowed Distal CBD by ERCP
(n = 38)
Biliary Drainage
(n = 18)
No Biliary Drainage
(n = 20)
Biliary-Enteric Anastamosis
(n = 13)
T-Tube Drainage
(n = 5)
Pseudocyst Drainage
(n = 9)
Medical Therapy
(n = 5)
Misc. Surgical Procedures
(n = 6)
1 Surgical Revision of CCJ to CDJ
2 Surgical Revisions to Biliary-Enteric Anastamoses
1 Required CC, CBDE, T-Tube Drainage

FIG. 5. Types of therapy received by 38 patients with intrapancreatic biliary strictures. CBD = common bile duct. CCJ = cholecystojejunostomy. CDJ = choledochoduodenostomy. CC = cholecystectomy. CBDE = common bile duct exploration.

Correlation of Laboratory Values with Cholangiographic Findings

To assess the potential predictive value of laboratory tests for cholangiographic findings, a simple linear regression analysis was performed, and correlation coefficients were determined between four variables (Table 3). There was no significant correlation of either the alkaline phosphatase or the total bilirubin levels with stricture length or proximal CBD diameter. Furthermore, there was no correlation of total bilirubin with alkaline phosphatase levels nor of stricture length with CBD diameter. The disparity between CBD configuration and laboratory values can be appreciated in Figures 1–4.

Hospital Course and Discharge Status (Table 4)

The average hospital stay was 41.7 days, with no difference between the patients who had BD compared with those who did not. The average alkaline phosphatase value at discharge had fallen to approximately 1.5 times normal, and the average total bilirubin level was normal. There was no difference in average discharge laboratory values in the patients who did not have BD compared with those who did.

Follow-up (Table 5)

Six patients were lost to follow-up, leaving 32 patients with an average follow-up period of 4.0 ± 1.0 years. The mean lengths of follow-up for the patients who had BD and for those who did not were 4.4 ± 0.9 and 3.8 ± 1.1 years, respectively. One patient died of acute mesenteric infarction 4.5 years after a cholecystectomy and choledochoduodenostomy. Eight patients had repeated episodes of pancreatitis. A pancreatic abscess developed in one patient 2.5 years after drainage of a pseudocyst, and one patient required drainage of a second pseudocyst. The remaining 16 patients had no further pancreatic or

TABLE 1. *Liver Biopsy Results*

Interpretation	N
Normal	5
Biliary stasis	5
Biliary stasis + cholangitis	3
Fatty change only	3
Biliary cirrhosis	3
Portal fibrosis only	2
Pericholangitis	1
Early micronodular cirrhosis	1
Necrotizing granulomas	1
Total	24

TABLE 2. *Comparison of Laboratory and Clinical Data in Patients with and without Operative Biliary Drainage**

	Drainage	No Drainage
Age (years)	48.0 ± 6.0	51.0 ± 10.0
Average alkaline phosphatase level (IU/L)	442.0 ± 121.0	260.0 ± 56.0
Average bilirubin level (mg/dl)	5.9 ± 1.6	3.1 ± 1.1
Stricture length (cm)	3.7 ± 0.7	4.1 ± 0.9
CBD diameter (cm)	1.8 ± 0.2	1.8 ± 0.4
Average length of follow-up (years)	4.4 ± 3.4	3.8 ± 4.4

* No statistically significant differences were noted.

TABLE 3. *Correlation of Laboratory Values with Cholangiographic Findings**

	Alkaline Phosphatase Level	Total Bilirubin Level	Stricture Length	CBD Diameter
Alkaline phosphatase level	1.000			
Total bilirubin level	0.350	1.000		
Stricture length	0.081	0.050	1.000	
CBD diameter	0.237	0.023	0.101	1.000

* No statistically significant correlations were noted.

biliary problems. The frequency of problems was of no greater significance in the patients who did not have BD.

Discussion

Biliary strictures as a consequence of chronic pancreatitis have long been recognized,[10] but until recently were considered unusual. With the increasing use of ERCP, strictures are being identified more frequently. A review of series published over the previous 10 years (Table 6) yields an incidence of biliary stricture in association with chronic pancreatitis in alcoholic patients of 5.7%, with a broad range from 2.7% to 45.6%.[1-3,11-13] Differences in criteria used for patient selection accounts for this wide variation. Currently, controversy remains regarding the natural history of intrapancreatic biliary strictures, the accuracy of preoperative diagnosis, and the appropriate course of treatment. Our study, which contains the largest number of reported patients with biliary strictures treated without surgery, has helped clarify a number of these issues.

The pathologic characteristic of these strictures is one of encasement of the intra- or peripancreatic bile duct in a progressively fibrotic pancreas,[14-17] with edema and inflammation of an acute pancreatitic episode often exacerbating the stricture. The clinical consequences of these strictures can in turn be variable. Many are asymptomatic, with transient or low-grade liver function test abnormalities. Acute episodes of pancreatitis can in turn prompt acute and sometimes sharp elevations of both the serum bilirubin and alkaline phosphatase levels.

The clinical diagnosis of an intrapancreatic common bile duct stricture in a patient with chronic alcoholic pancreatitis is often difficult. There are no definitive signs or symptoms, and liver function test abnormalities may be suggestive but nonspecific. An acute or chronic elevation of the serum alkaline phosphatase level is the most frequent laboratory abnormality, occurring in approximately 80% of patients (Table 6).[3,5] The total serum bilirubin level is also frequently elevated during the acute episodes of pancreatitis, occurring in approximately 65% of patients (Table 6), returning to normal as the acute process subsides, and rarely remaining elevated on a chronic basis.[3,7,14,16,18] Cholangiography, either endoscopic or transhepatic, is the definitive diagnostic tool. Cholangiographic findings, however, are variable, as has been shown in this study and by others.[6,12,14] Previous publications have described these strictures as gradual taperings of the intrapancreatic duct over a distance of 3–5 cm, thereby distinguishing them from the abrupt, short obstructions seen in pancreatic cancer. The exceptions to this rule are sufficiently frequent to render cholangiographic findings dubious in the distinction of these two disease processes.[12]

The correlation of cholangiographic findings with liver function test (LFT) abnormalities was very low in this study, as others have also found.[7,12] In the patients from our study, long strictures with dilated proximal common bile ducts were present despite normal LFTs, whereas short strictures with normal proximal biliary anatomy were seen with remarkably elevated LFTs.

Once a biliary stricture is discovered, the remaining

TABLE 4. *Comparison of Hospital Course and Discharge Laboratory Values in Patients with and without Operative Biliary Drainage*

	Drainage	No Drainage
Length of stay (days)	42.0 ± 4.4	41.0 ± 4.6
Average discharge alkaline phosphatase level (IU/L; normal: 21–91 IU/L)	150.0 ± 39.0	154.0 ± 19.0
Average discharge total bilirubin level (mg/dl; normal: 0.1–1.0 mg/dl)	1.2 ± 0.4	0.9 ± 0.2

TABLE 5. *Comparison of Long-term Results in Patients with and without Operative Biliary Drainage*

	Drainage	No Drainage
Lost to follow-up	3	3
Length of follow-up (years)	4.4 ± 0.9	3.8 ± 1.1
Deaths	1	0
Repeated episodes of pancreatitis	3	5
Initial treatment failures	3	1
Repeat pseudocyst drainage	0	1
Late pancreatic abscess	0	1
No further problems	7	9

TABLE 6. *Literature Review of CBD Stricture Characteristics in Patients with Chronic Pancreatitis*

First Author	No. of Patients	Elevated Bilirubin Level	Elevated Alkaline Phosphatase Level	Incidence of Cholangitis	Incidence of Biliary Cirrhosis	Incidence of CBD Stricture In All Cases Pancreatitis (%)
McCollum (1975)[20]	7	7/7	—	—	—	—
Warshaw (1976)[4]	6	6/6	6/6	3/6	3/4	—
Scott (1977)[2]	11	9/11	10/11	—	1/11	11/38*
Schulte (1977)[5]	13	8/13	13/13	4/13	—	—
Sarles (1978)[6]	—	—	—	—	0/300	—
Bradley (1978)[18]	13	—	—	2/13	—	—
Gremillion (1979)[14]	7	5/7	7/7	0/7	—	—
Yadegar (1980)[3]	21	13/21	20/21	3/21	2/11	21/651†
Gregg (1981)[7]	21	11/21	11/21	—	0/21	—
Afroudakis (1981)[1]	24	—	—	—	4/24	8/300‡
Creaghe (1981)[15]	10	—	—	1/10	2/10	—
Wisloff (1982)[13]	36	19/36	26/36	—	—	36/79§
Eckhauser (1983)[16]	9	5/9	9/9	0/9	—	—
DaCunha (1984)[8]	45	—	—	3/45	—	—
Aranha (1984)[11]	51	44/51	48/51	3/51	0/51	51/1262‖
Petrozza (1985)[12]	15	—	14/15	—	—	15/151¶
Sugerman (1986)[19]	16	—	—	1/16	—	—
Current study	38	19/38	24/38	1/38	3/24	—
Total (%)	343	146/220 (66.3%)	188/228 (82.5%)	21/229 (9.2%)	15/456 (3.3%)	142/2481 (5.7%)

* Of 38 patients with chronic alcoholic pancreatitis, 11 were found to have intrapancreatic CBD strictures by ERCP.

† Of 651 admissions for chronic alcoholic pancreatitis from January 1968 through December 1979, 21 patients had surgery for intrapancreatic CBD strictures.

‡ Of 300 patients with chronic alcoholic pancreatitis from 1972 through 1979, 24 were found to have intrapancreatic CBD stricture.

§ Of 79 consecutive patients with moderately severe chronic pancreatitis who had ERCP, 36 were found to have stenosis of the intrapancreatic CBD.

‖ Of 1262 patients with chronic pancreatitis admitted from 1970 through 1982, 51 of these patients were treated for distal CBD obstruction.

¶ Of 151 patients admitted for chronic alcoholic pancreatitis from 1979 through 1984, 15 were found to have a stricture of the intrapancreatic CBD by cholangiography.

decisions involve the proper therapeutic choice(s). Concerns over the possible development of acute cholangitis and/or biliary cirrhosis have in the past prompted *early* surgical drainage of the proximal biliary tree.[4,5] More recent recommendations are to delay drainage until problems manifest themselves.[3,6,7,15,16] This latter approach is supported by low rates for cholangitis and biliary cirrhosis reported by ourselves and others (Table 6).

The decision to delay drainage of a CBD stricture due to pancreatitis must be based on an assessment of the risk in conservative or expectant management of this lesion. Although no study specifically addresses nonsurgical treatment of biliary strictures in chronic pancreatitis, there are small cohorts of patients who for various reasons did not have surgical therapy of their biliary strictures.[1-3] Scott et al.[2] reported on 11 patients with chronic alcoholic pancreatitis and intrapancreatic CBD strictures. Five of these patients had no surgery, and for a follow-up of 1 year or more, had no further problems. Yadegar et al.[3] followed two patients with known strictures and chronic elevations of alkaline phosphatase levels for 5 years, obtaining several subsequent liver biopsies. No disease progression was discovered in either patient histologically or clinically, and there was no mention of the occurrence of cholangitis. Afroudakis and Kaplowitz[1] reviewed liver histology from 24 patients with known CBD strictures due to chronic alcoholic pancreatitis, and found that three of these patients had disease progression to biliary cirrhosis over an unspecified period after the initial diagnosis. Our study contains the largest single collection of patients with known biliary strictures who did not have surgical therapy. These 20 patients were followed for an average of 3.8 years with no increased morbidity compared with those patients initially undergoing BD, despite clinical and cholangiographic disease of comparable severity.

Based on the above findings, we believe that the presence of a stricture should not be the sole indication for surgical intervention. Absolute indications for surgical intervention are acute cholangitis, biliary cirrhosis, and protracted jaundice.[3,4,7,8,14-16,19,20] Based on previous and current findings, there are two relative indications for operative biliary drainage: in patients with diagnosed strictures in whom a pancreatic procedure is already planned,[7] and in patients with known strictures and a previous history of cholangitis. The presence of a dilated CBD proximal to a stricture and/or a chronically elevated alkaline phosphatase level do not justify surgical intervention, but most certainly warrant long-term follow-up consisting of periodic liver function tests, cholangiography, and liver biopsies.[3,16] Once operative biliary drainage is indicated, we recommend choledochoenterostomy over cholecystoenterostomy or T-tube drainage. Results of our study and of others suggest that cholecystoenterostomy does not offer sufficient or reliable long-term drainage.[3,5,7,8,14] Prolonged T-tube drainage in two of five patients in our study necessitated revisions to choledochoenterostomies. This problem has also been reported by others.[4,14]

In summary, we present 38 patients with chronic alcoholic pancreatitis and ERCP-proven intrapancreatic biliary strictures. Twenty of the 38 patients did not have surgical therapy, with no increase in morbidity compared with the 18 patients who had surgery, despite disease of equivalent severity. Based on these findings, we believe that asymptomatic biliary strictures in patients with chronic pancreatitis can be safely observed, with periodic evaluation using liver function tests, ERCP, and liver biopsies. Absolute indications for surgery are acute cholangitis, biliary cirrhosis, and persistent jaundice. Relative indications for biliary drainage include a planned pancreatic procedure and a previous history of cholangitis in a patient with a known stricture.

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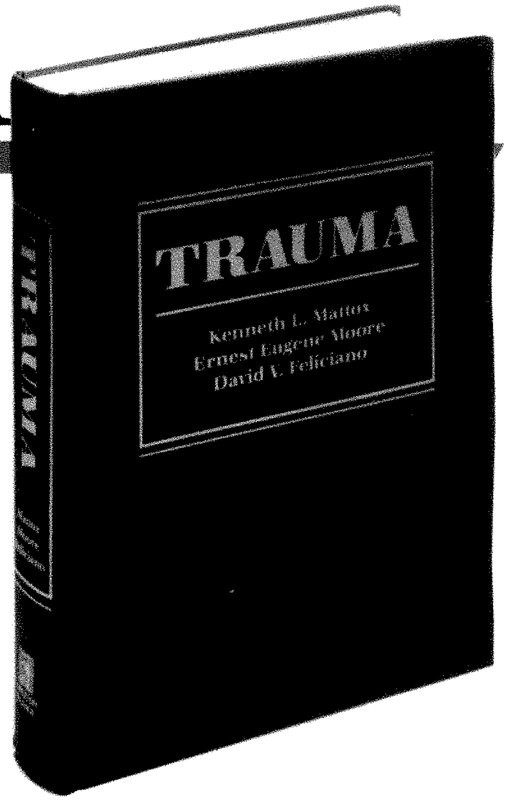

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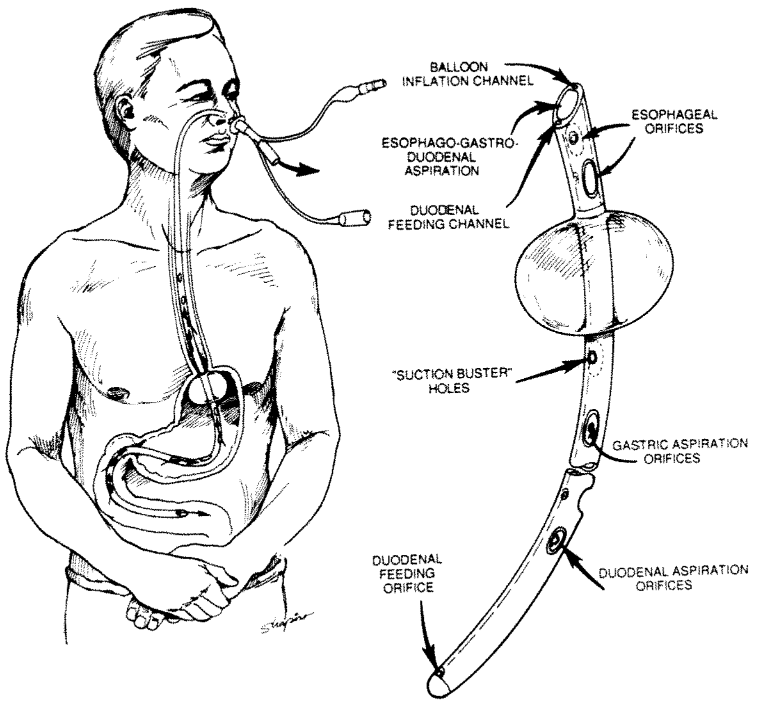
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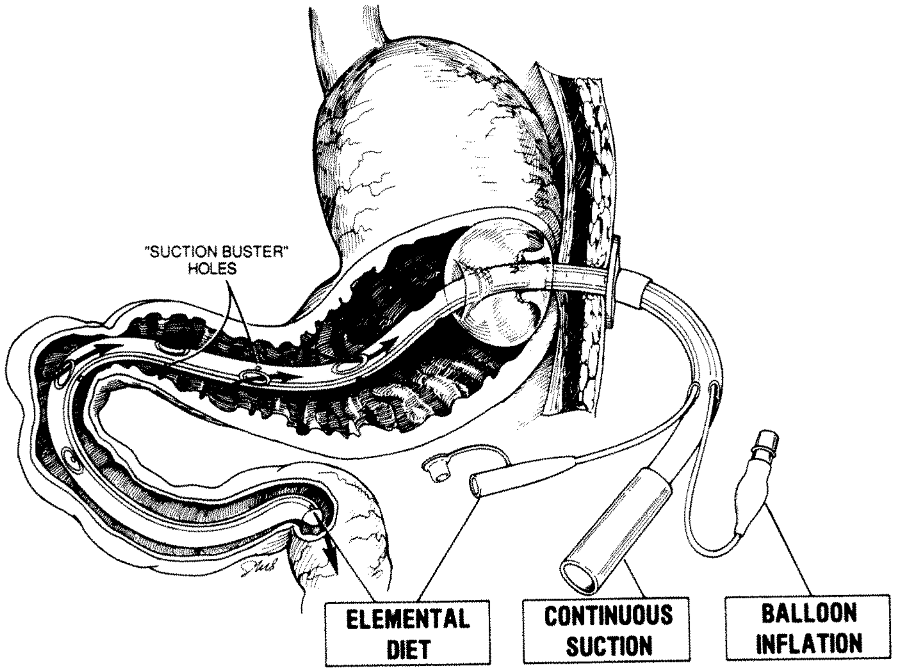

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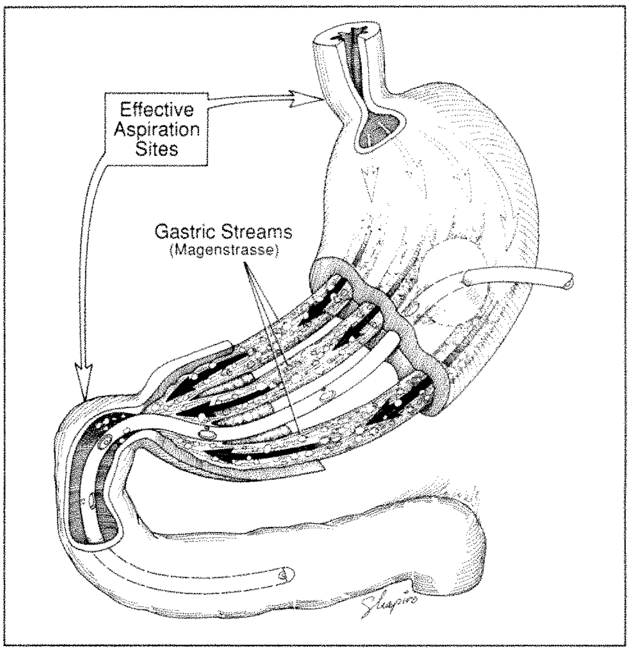

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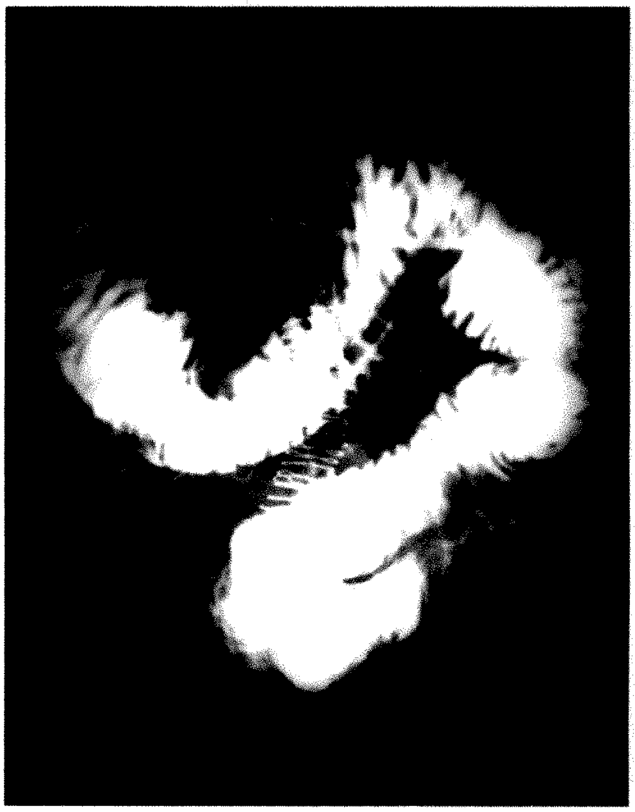

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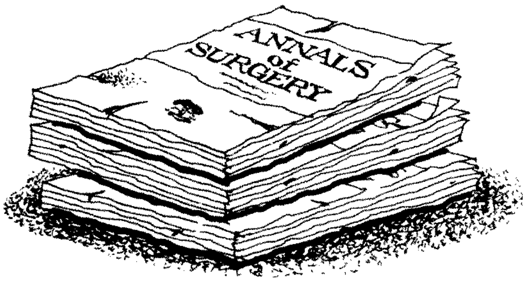

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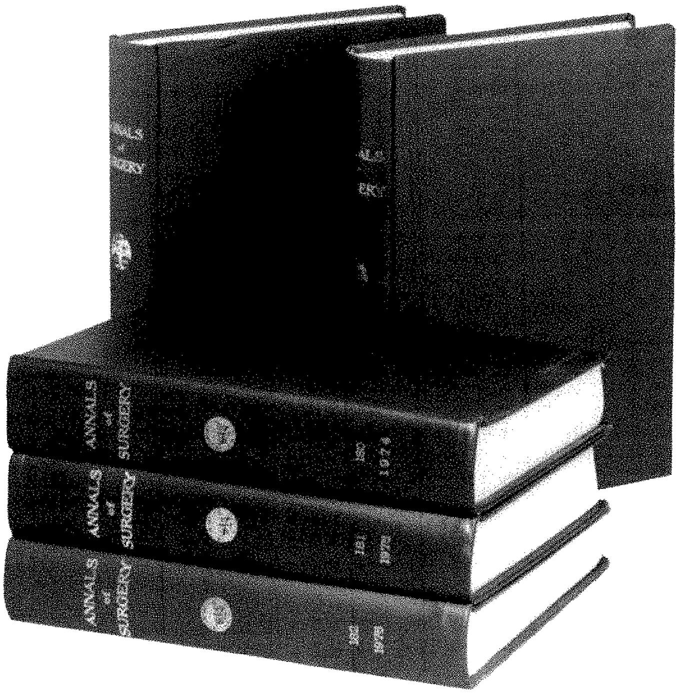

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This study quantifies lung water in acute hemorrhagic pancreatitis to determine the degree to which pulmonary dysfunction occurs subclinically, before alterations in the arterial blood gases can be measured. Pancreatitis was induced in ten dogs by injecting 0.5 ml/kg of bile into the pancreatic ducts, which had been surgically cannulated. Pulmonary and systemic blood gases and blood pressures, heart rate, extravascular lung water, and lung blood flows were studied over 5 hours while cardiac output and mean arterial pressure were maintained at control values by Ringer's lactate infusion. The percentage of water in lung tissue was determined at the time of sacrifice using gravimetric measurements. Mean arterial pressure, cardiac output, and pulmonary capillary wedge pressure, reflecting intravascular volume status, did not change through at the experiment. By contrast, major disturbances were measured in the pulmonary bed with pulmonary artery pressures rising from 15.6 ± 1.8/8.1 ± 1.3 mmHg to 22.0 ± 1.2/15.6 ± 1.7 mmHg over 5 hours ($p < 0.01$). Peripheral vascular resistance rose from 3.6 ± 0.6 units to 6.6 ± 0.4 units ($p < 0.05$), whereas bronchial blood flow to the lung fell significantly. These changes in pulmonary hemodynamics were not reflected by changes in the arterial blood gases. Arterial oxygenation was maintained during 5 hours of pancreatitis. The partial pressure of carbon dioxide and the serum pH did not change significantly. There was, however, a progressive rise in extravascular lung water measured by the double-dilution technique from 10.2 ± 0.8 ml/kg at control to 18.1 ± 2.8 ml/kg ($p < 0.01$) at 5 hours. This was confirmed by direct gravimetric measurements, which revealed an increase in the water content of the lung from 78.1 ± 0.3% to 86.4 ± 2.4% over the course of the experiment. Arterial blood gases, therefore, do not necessarily reflect the pulmonary deterioration in acute pancreatitis. These data supported a mechanism of lung dysfunction independent of the circulatory compromise, which often accompanies the disease in the clinical setting.

IN HEMORRHAGIC PANCREATITIS, serious lung complications occur in over 50% of patients.[1,2] The respiratory dysfunction that accompanies the disease can range from a mild oxygenation defect to a fatal adult respiratory distress syndrome. Patients with acute pancreatitis may have massive third-space sequestration of fluid and usually present in moderate to severe hypovolemic states. Whether the pulmonary deterioration in pancreatitis results from the response of the lung to circulatory compromise, which effects patients before fluid resuscitation, or to humoral and reflex effects specific to the injured pancreas is unknown. The respiratory defect is usually first signaled clinically by aberrations in arterial blood gases and later by changes in the chest radiograph. This study involved the measurement of lung water in a canine model of pancreatitis to determine whether, in the absence of the usual clinical signs of lung dysfunction, significant occult derangement of pulmonary physiology occurs. By strictly maintaining hemodynamic parameters at control values from the onset of the pancreatic insult, we attempted to resolve whether the pulmonary defect emanates from hypovolemia and shock or from mechanisms unique to pancreatitis.

Methods and Materials

Ten large mongrel dogs (mean weight: 23.4 ± 1.5 kg) were housed for several days in individual cages until a normal complete blood count and a negative screen for microfilaria were obtained. All animals were free from acute gastrointestinal and upper respiratory disease. The animals were allowed water intake *ad libitum* but no food starting 12 hours before the experiment. After sedation with intramuscular acepromazine (0.005 mg/kg), a peripheral venous catheter was placed. Intravenous sodium pentobarbital (15 mg/kg) was administered to induce anesthesia. Each dog was incubated and allowed

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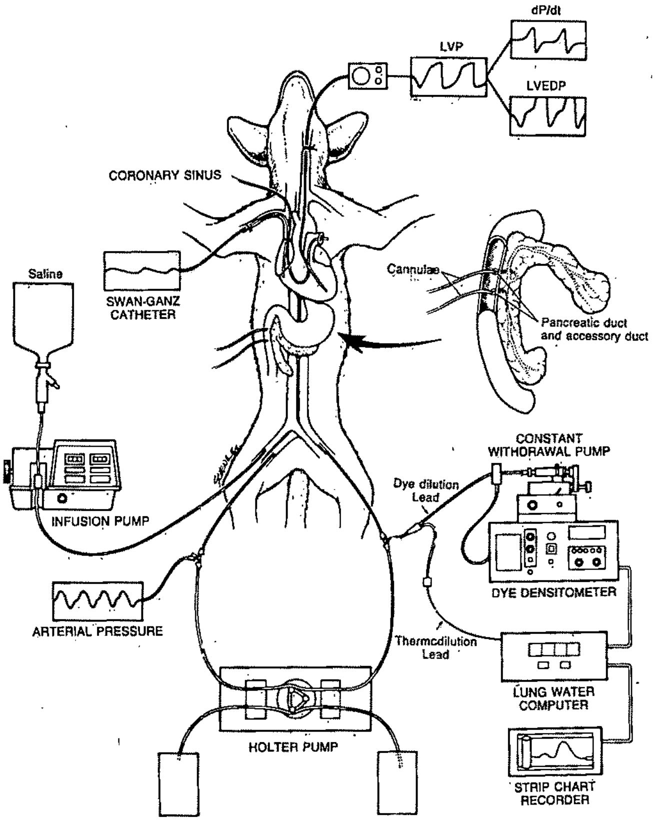

FIG. 1. Instrumentation of a dog before induction of pancreatitis.

to breath spontaneously. Alpha-chloralose (50 mg/kg) in solution with polyethylene glycol 200 was given intravenously to maintain anesthesia. Supplemental doses were used as necessary over the course of the experiment.

Each animal was instrumented as indicated in Figure 1. A 16-gauge catheter was placed in the femoral vein for fluid administration and blood withdrawal. Both femoral arteries were catheterized for continuous blood pressure recording (Statham pressure transducer, Model P23ID, Statham Gould Medical Products Division, Oxnard, CA, and Siemen's micrograph recorder, Model 81, Siemens, Iselin, NJ) and for simultaneous blood withdrawal for use in regional blood flow measurements with the microsphere technique. A microtipped, pressure-sensitive transducer (#7 French, Model CP470, Millar Instruments, Inc., Houston, TX) was introduced into the left ventricle by retrograde cannulation of the left common carotid artery for injection of microspheres and for measurement of left heart pressures.

The right femoral artery was cannulated with an Edwards Laboratory lung water catheter (Model 96-020-5F). This catheter was attached to a Gilford syringe pump (Model 105-S) to allow blood withdrawal through the cardiac output dye-densitometer (Waters Instruments, Model COR-100, Waters Instruments, Rochester, MN) during extravascular lung water determination. A balloon-tipped Swan-Ganz catheter (Model 93A-831H-7.5F, American Edwards, Division of American Hospital Supply, Irvine, CA) was threaded *via* the left internal jugular vein through the right side of the heart and into the pulmonary artery. Its position was confirmed initially by fluoroscopic examination and subsequently by wave form monitoring. Systemic anticoagulation was induced by the administration of intravenous heparin (100 units/kg) and maintained with supplemental doses of 50 units/kg/h.

Intravenous lactated Ringer's solution was begun (10 ml/kg) during instrumentation to account for overnight volume depletion from fasting. Each dog underwent celiotomy through a midline incision. An anterior enterotomy was made in the second portion of the duodenum. The main and accessory pancreatic ducts were individually cannulated with long 20-gauge catheters that were secured with silk pursestring sutures. Bile was withdrawn from the gallbladder by direct needle puncture of the organ and injected (0.5 ml/kg) into the main pancreatic duct. This was performed under direct vision to assure bile staining of the entire pancreas and to verify no leakage from the ampullae. The catheters were occluded with stop cocks and left in place in the abdomen. The duodenal and abdominal incisions were closed. Animals were followed for 5 hours after the induction of pancreatitis.

Control and systemic blood pressures, heart rate, pulmonary wedge pressure, and cardiac output using both the thermodilution and cardiogreen dye dilution techniques were measured before the induction of bile pancreatitis. Stroke volume was determined from heart rate and cardiac output. Pulmonary vascular resistance was calculated. During 5 hours of pancreatitis, these parameters were studied hourly. In addition, cardiac output and systemic blood pressures were measured every 15 minutes so that the rate of lactated Ringer's administration could be adjusted to maintain these parameters at control levels.

Pulmonary and peripheral artery blood gases were measured (Model ABL-3, Radiometer American Inc., Dallas, TX) before the induction of biliary pancreatitis and hourly thereafter. Amylase and creatinine levels were measured during the control period and at 2 and 5 hours to assure the production of a significant pancreatic injury and to obtain some indication of the state of hydration of the animal.

Two methods of measuring lung water were used. In the double-indicator dilution technique described by Lewis and Elings,[3] a cardiogreen dilution curve was compared with the dilution curve of iced saline by a microprocessing digital computer (American Edwards Laboratory Lung Water Computer, Model 9310) to determine the size of the extravascular fluid compartment in the lungs. In addition, the dry/wet weight ratio of normal dog lung was compared with that of dogs 5 hours after the induction of bile pancreatitis to show the change in percentage of water of the pulmonary parenchyma.

Nutritive lung blood flows were measured hourly using a microsphere technique. Six radioactive labels, I-125, Nb-95, Sc-46, Sr-85, Co-57, and Sn-113 (New England Nuclear, Boston, MA), measuring 15 μm in diameter were used. For each measurement of flow, a bolus of labeled microspheres (approximately 1.5 million) was injected into the left ventricle and the catheter flushed with 10 ml of warm saline. Simultaneous with the injection of microspheres and continuing for 120 seconds, duplicate reference blood samples were obtained from the femoral arteries at a constant withdrawal rate of 12 ml/min (Holter Pump, Model 911, Critikon Laboratories, Tampa, FL). Five hours after the induction of pancreatitis, the animals were killed by an overdose of barbituates according to the guidelines set by the National Institutes of Health and by the University of Texas Health Science Center Faculty Committee for Animal Use. Lung and kidney tissue was harvested, and blood and tissue samples were weighed to the nearest milligram and counted for 5 minutes in a multichannel autogamma scintillation spectrometer (Model 5320, Packard Instrument Co., Laguna Hills, CA). For each set of samples, vials containing aliquots of each microsphere were used to determine the energy level setting on the scintillation counter. From the standards of each microsphere used to set the energy level and the blood samples containing the highest count of microspheres injected, the cross-talk fraction or overlap of gamma energy was calculated for each of the microspheres. The contribution of overlap of gamma energy of each microsphere was subtracted and a nuclide reference factor (ml/min/count) was calculated. For each tissue sample, the background counts were subtracted and the counts for each isotope were multiplied by the nuclide reference factor to obtain mean blood flow rate. Only animals with less than 15% disparity between right and left kidney flows were used for data analysis. Flows were calculated using a DEC-10 computer program (Digital Equipment Corporation, Maynard, MA) and expressed as ml/min/g.

At autopsy the gross appearance of the lung was noted and tissue for dry/wet weight ratios and blood flow studies was harvested. The proper placement of intrathoracic catheters was verified. In the abdomen, the bowel was examined and the presence and quantity of ascites were noted. The appearance of the pancreas and retroperitoneum with respect to hemorrhage, necrosis, accumulation of edema, and tissue saponification was recorded.

TABLE 1. *Systemic Hemodynamic and Metabolic Parameters*

	Control	2-Hour	5-Hour
MAP (mmHg)	88 ± 5	89 ± 9	92 ± 8
HR (beats/min)	110 ± 5	102 ± 5	102 ± 6
CO (ml/kg/min)	131 ± 7	162 ± 15	128 ± 9
Stroke volume (ml/kg)	1.18 ± 0.09	1.28 ± 0.11	1.26 ± 0.13
PCWP (mmHg)	5.3 ± 0.6	5.7 ± 1.6	5.6 ± 0.4
Amylase (mg/dl)	631 ± 77	3575 ± 1644*	1505 ± 223*
Creatinine (mg/dl)	1.0 ± 0.1	1.1 ± 0.9	1.0 ± 0.1
Hgb (g/dl)	12.2 ± 0.6	10.3 ± 0.9	8.3 ± 0.5*

* Significant difference from control, $p < 0.05$.

All data are presented as mean ± SEM. A two-way analysis of variance and a Newman-Keuls test were used to evaluate significant differences between groups with regard to hemodynamic and metabolic parameters and changes in regional blood flow. Differences were considered significant at $p < 0.05$.

Results

Systemic Hemodynamics

Over the 5 hours after induction of pancreatitis, hemodynamic parameters were maintained at control values by crystalloid administration. The mean arterial pressure was stable near the control value of 88 ± 5 mmHg and the heart rate did not change significantly over the course of the experiment from the prepancreatitis value of 110 ± 5 beats/min (Table 1). Similarly, despite the extensive third-space fluid losses common in hemorrhagic pancreatitis, cardiac output and stroke volume were kept constant by lactated Ringer's solution infusion. The pulmonary capillary wedge pressure, an indicator of left ventricular filling pressure and preload, was not altered from the control level of 5.3 ± 0.6 mmHg, demonstrating the stable intravascular volume status throughout the experiment.

Metabolic Indicators of Pancreatitis

The metabolic data are also presented in Table 1. The gross alterations in the pancreas seen directly after injection of autologous bile into the pancreatic duct were reflected by rising serum amylase levels. The amylase level rose 467% by 2 hours and was still 139% above control levels at 5 hours after the induction of pancreatitis. The creatinine level was unchanged from the control value of 1.2 mg/dl over that period. Neither arterial pH nor serum bicarbonate levels were altered over the course of 5 hours, indicating an absence of significant uncompensated acidosis after the pancreatic insult. The hemoglobin level, however, fell to 84% of control values by 2 hours and was 68% of the peak prepancreatitis value at 5 hours ($p < 0.05$).

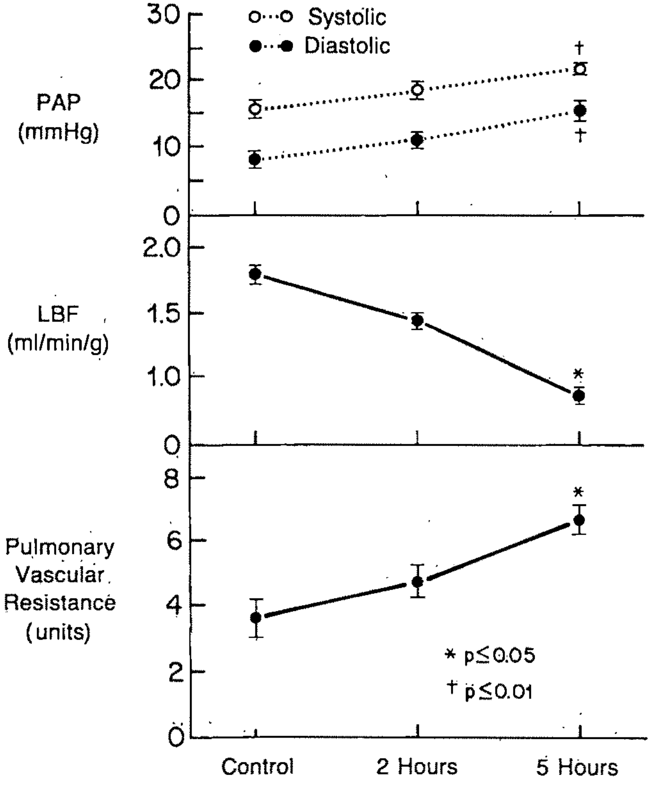

FIG. 2. Pulmonary hemodynamics over 5 hours after the induction of pancreatitis. †p ≤ 0.01; *p ≤ 0.05.

Pulmonary Hemodynamics

Whereas systemic cardiovascular parameters were largely unchanged over 5 hours of pancreatitis, major hemodynamic disturbances were measured in the pulmonary system (Fig. 2). Pulmonary artery systolic pressures rose 41% and diastolic pressures rose 93% over the course of the experiment, and this elevation reached significance at 5 hours. Pulmonary vascular resistance was elevated by 2 hours and continued to rise until the end of the study when an 83% increase above control levels was noted. A concomitant fall in lung blood flow, to 46% of control values, was measured at 5 hours ($p < 0.05$).

Gas Exchange and Extravascular Lung Water

Although significant changes in the hemodynamic functions of the lung were measured, the diffusing capacity of the lung was not greatly impaired over 5 hours of pancreatitis, as demonstrated in Table 2. Partial pressure of oxygen did not change significantly from the control value of 111 ± 8 mmHg. There was a slight but not significant decrease in partial pressure of carbon dioxide over the course of the experiment. Pulmonary artery oxygen content was maintained over the initial 2 hours of the study, but fell significantly to 76% of control values by 5 hours. This most likely reflects the increased oxygen extraction in the periphery from the stress of the pancreatic insult.

TABLE 2. *Arterial Blood Gases*

	Control	2-Hour	5-Hour
pH	7.32 ± 0.03	7.34 ± 0.03	7.30 ± 0.04
pO_2 (mmHg)	111 ± 8	120 ± 10	111 ± 10
pCO_2 (mmHg)	35 ± 3	32 ± 2	31 ± 1

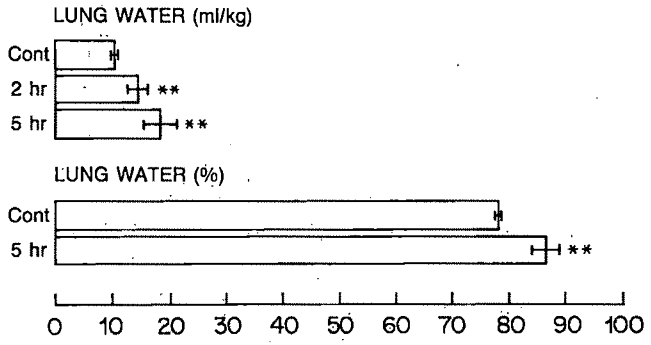

FIG. 3. Extravascular lung water and water composition of pulmonary parenchyma over 5 hours of pancreatitis. *p < 0.05; **p < 0.01.

Despite the lack of impairment of pulmonary gas exchange, extravascular lung water measured by double dilution curves increased progressively from the control value of 10.2 ± 0.8 ml/kg over the 5-hour study (Fig. 3). The 40% rise in extravascular water noted at 2 hours reached significance at the $p \leq 0.05$ level, whereas an 80% rise over control ($p < 0.01$) was measured at 5 hours. The rise in lung water was confirmed by the altered dry/wet ratios of lung tissue at sacrifice.

Autopsy Findings

No animal died before completion of the study. The postmortem examinations of animals with autologous bile-induced pancreatitis revealed several abnormalities. All animals showed gross evidence of acute pancreatitis with changes in the pancreatic bed. The retroperitoneum was massively edematous in all animals, with pancreatic hemorrhage and frank saponification noted in nine of 10 animals. Dilated, boggy small bowel and acites were present in all dogs at sacrifice, with more than half the animals sequestering over 500 ml of intraperitoneal fluid.

Frank pulmonary consolidation was evident in all animals with dependent areas of the lungs being the most affected. Despite the low pulmonary capillary wedge pressures measured, nine of 10 animals had frothy sputum evident in the endotracheal tube at or before sacrifice.

Discussion

The quantification of extravascular lung water was described 30 years ago by Chinard and Enns,[4] who used a technique of measuring the diffusion of radioactive isotopes into the pulmonary parenchyma. This method correlated poorly with actual gravimetric measurements of lung water, however, because of slow molecular diffusibility, especially with extensive pulmonary edema. Another drawback of the technique was that accuracy varied greatly with changes in cardiac output. In the 1970s, extravascular lung water was quantified with double-indicator dilution techniques using thermal dilution,[5–7] which is a hundred times faster than molecular diffusion.[3] This method had the benefit of being reproducible, repeatable without blood loss, nontoxic, and had minimal[8,9] or no[10] dependence on filling pressures and cardiac output. The clinical applicability of the method was restricted, however, as the curves for thermodilution and green dye dilution required integration and comparison by hand. With the development of the microprocessing digital computer that performed the cumbersome mathematics, Lewis and Elings[3] advanced a technique for measuring extravascular lung water that could be carried out easily and rapidly at the bedside. The reproducibility of multiple green dye thermodilution determinations of extravascular lung water is within 8%.[11] Some studies have suggested a slight overestimation (10–20%) of extravascular lung water by double-dilution techniques because of the similar heat diffusion capacities of certain nonaqueous lung tissues[13,14]; however, other studies have failed to confirm these data.[10] Regardless of this disagreement, the measurement using double-dilution methods mimic those of lung water by gravimetric techniques with a correlation coefficient of greater than 0.9.[10,12,15–17]

Enquist and Gliedman[18] reported that respiratory failure was the cause of death in 20% of patients dying of acute pancreatitis, and pulmonary disease contributed to the death of another 40% of such patients. Despite the initial paucity of roentgenographic and clinical findings of pulmonary failure in patients with acute pancreatitis, a mild to moderate degree of respiratory insufficiency may be demonstrated in over half the patients by measuring the arterial blood gases.[19] We have attempted to demonstrate that the pulmonary changes involved in the disease process occur long before aberrations in gas diffusion can be measured.

Our study confirms the hemodynamic derangements of the pulmonary bed that have been reported by others in acute pancreatitis.[20–22] A significant pulmonary hypertension is noted along with a major rise in vascular resistance and a decrease in the bronchial blood flow to the lung. In this study, all of these conditions are noted within 2 hours of the onset of the pancreatic insult and often as early as 30 minutes after the induction of pancreatitis; abnormal gas exchange was still not detected 5 hours after the onset of pancreatitis.

The rise in extravascular lung water, measured noninvasively by the double indicator dilution technique, likewise occurred in rapid sequence after the onset of pancreatitis. This increase in extravascular lung water was progressive and appeared unrelated to left ventricular filling pressures. Although elevated pulmonary capillary wedge pressures in pancreatitis have been reported sporadically,[22,23] the larger body of experimental and clinical work confirmed the low or normal values reported in this study.[21,24–26] The gross pulmonary edema of pancreatitis, which was noted in 90% of the dogs in this study, has been studied by Warshaw et al.[25] and Lee et al.[21] The lung edema of pancreatitis is an exudative fluid with a high protein content, which further supports an increase in pulmonary endothelial permeability rather than a transudative, pressure-related phenomenon.

The mechanism of injury to the capillary alveolar membrane in pancreatitis is not well delineated. Clearly, the accumulation of excess extravascular lung water in pancreatitis is not solely related to hypovolemia and shock, which was prevented in this canine model, nor to a hypoxic injury, since the partial pressure of oxygen never fell during the current study. The release of lecithinase (phospholipase A) from the pancreas with the subsequent destruction of pulmonary surfactant and the development of atelectasis and fluid exudation has been proposed[27–29] as a mechanism of injury. Elevated triglycerides and their breakdown to free fatty acids, which have a toxic effect at the alveolar level, have been implicated in the pulmonary injury of pancreatitis.[25,30,31] Bradykinin and kallikrein, vasodilatory substances believed to be activated by the release from the pancreas of trypsinogen and kallikreinogen during the acute phases of pancreatitis, may play a role in the systemic effects of pancreatitis.[32,33] The above-mentioned mechanisms of pulmonary insult are all direct; that is, the injury would appear to be a result of direct contact between an offending substance and the lung. The role of indirect mechanisms of pulmonary injury, that is, those requiring the participation of an intermediary such as polymorphonucleocytes or complement, is still largely unknown in acute pancreatitis.[34]

Extravascular lung water measurement requires nothing more invasive than the usual minimal monitoring devices in a critically ill patient, *i.e.*, central venous access and a peripheral artery line. Whether this technology develops into a useful clinical adjuvant for signaling pulmonary dysfunction earlier in the course of pancreatitis than do the arterial blood gases currently remains to be seen. As of now, the quantification of extravascular lung water remains a sensitive research tool for the monitoring of pulmonary dysfunction in a variety of disease states.

Summary

From this study it is clear that the respiratory deterioration in hemorrhagic pancreatitis results not from the response of the lung to hypovolemia and shock but from humoral or reflex effect specific to the diseased pancreas. Although mean arterial pressure, cardiac output, and pulmonary capillary wedge pressure were maintained at control values, major hemodynamic disturbances were noted in the pulmonary bed. These included a rise in pulmonary vascular resistance, a fall in the nutritive blood flow to the lung, and a significant pulmonary hypertension. These changes were not reflected in the arterial blood gases, which showed that partial pressures of oxygen and carbon dioxide were maintained at control values, as was the acid-base status of the animal. Lung water, measured using two different methods, rose progressively over the first 5 hours of pancreatitis, demonstrating clearly that the arterial blood gases do not necessarily reflect the pulmonary deterioration early in the course of acute pancreatitis.

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The Complications of Pancreatectomy

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This paper analyses the early postoperative complications after 285 pancreaticoduodenectomies performed during the past 15 years in the Surgical University Clinic, Mannheim. There were 235 partial (Whipple) and 52 total pancreatectomies performed for pancreatic and periampullary tumors (181 patients) and complicated chronic pancreatitis (104 patients). A total of 92 complications requiring relaparotomy in 42 patients ended fatally in nine patients. The overall operative and hospital mortality rate was 3.1%. The most frequent and most dangerous were complications at or around the pancreaticojejunal anastomosis, which occurred 25 times with five deaths. Postoperative hemorrhage was seen in 16 patients; endoscopic treatment in four patients and operation in 12 patients was successful in stopping the bleeding in all but one patient. Eight biliary fistulae either ceased spontaneously (3 patients) or after operative reintervention (5 patients) without any mortality. Control of these complications depends on four lines of approach: (1) *before* operation: optimal preparation of the jaundiced patient including endoscopic transpapillary decompression of the common duct; (2) *during* operation: a meticulous and standardized technique is mandatory; (3) *after* operation: continous observation in the surgical intensive care unit is essential for the timely detection of possible complications; and (4) early reintervention can salvage the great majority of these patients with deleterious complications.

EVEN IN THE LAST QUARTER of the 20th century, pancreatectomy remains one of the most formidable abdominal operations for the surgeon. Originally performed in 1909 by Kausch in Berlin,[1] it was perfected and popularized by Whipple in 1934,[2] and has since found its way into most surgical departments all over the world. Lionized by some surgeons as the "cadillac of abdominal surgery,"[3] morbidity and mortality of this operation are so formidable that others have abandoned it altogether.[4,5] Yet, others (albeit not very seriously) are trying to have it banned by law.[6]

In this paper we intend to take on this argument by analysing the postoperative complications after 285 pancreatectomies. The lessons we learned from this experience hopefully will be of some use to the reader.

Materials and Methods

To put these complications into perspective, the overall results of 285 pancreatectomies are presented in Table 1. The operations were performed at the Surgical Clinic of Mannheim (Heidelberg University) between October 1972 and April 1987. There were 172 men and 113 women. The age of these patients ranged from 23 to 75 years with a median of 53 years.

The indications for pancreatectomy in two thirds of all operations were for adenocarcinoma of the pancreas or periampullary malignancy. The preferred procedure was the Whipple operation. Total pancreatectomy was required in only 20% of these cases for reasons of radicality.

In cases where severe and complicated chronic pancreatitis was centered in the head of the pancreas, the Whipple procedure was effective in removing obstruction (of the duodenum, pancreatic, and bile ducts) and pain. Total pancreatectomy was reserved for patients with end-stage chronic pancreatitis early on in the period and has been all but abandoned for this indication since 1976. The details of our technique have been published previously.[7]

Nine patients died after operation in the hospital, for an overall mortality rate of 3.1%. The longest series of operations performed without any mortality were 75 consecutive Whipple procedures done between June 1976 and November 1981.

Although these results appear encouraging, the post-

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TABLE 1. *Early Results of Duodenopancreatectomy in 285 Patients*

Type of Procedure	No. of Patients	Diagnosis: Neoplasm	Diagnosis: Pancreatitis	Operative Hospital Mortality
Whipple operation	233	146	87	6
Total pancreatectomy	52	35	17	3
Total	285	181 (7 deaths)	104 (2 deaths)	9 (3.1%)

operative course has not been smooth all the way. On the contrary, Table 2 shows that a total of 92 complications occurred of which 42 required relaparotomy. These complications will now be analysed in detail.

Nonsurgical Complications

There were 26 major nonsurgical complications, which are listed in Table 3. These mainly concerned pulmonary, cardiac, and hepatic problems. The latter consisted solely of transient laboratory findings (elevated transaminate levels) in jaundiced patients. In this series of 285 pancreatectomies there was not one case of postoperative renal failure or so-called hepatorenal syndrome.

The one death from bronchopneumonia occurred on the 14th postoperative day in a 49-year-old man who had total gastrectomy as well as total pancreatectomy performed for a gastric carcinoma infiltrating the pancreas. The cause of death was probably aspiration pneumonia since the abdominal findings at autopsy were normal. One 75-year-old man died of myocardial infarction after an uneventful total pancreatectomy for cancer. Another patient died of venous catheter sepsis 12 days after total pancreatectomy for end-stage chronic pancreatitis.

TABLE 2. *Complications after 285 Partial and Total Pancreatectomies*

	Whipple Operation (N = 233)	Total Pancreatectomy (N = 52)
Complications (N = 92)	72 (32%)	20 (40%)
Relaparotomies (N = 42)	38 (17%)	4 (8%)
Deaths (N = 9)	6 (2.7%)	3 (6%)

TABLE 3. *Major Nonsurgical Complications after 285 Pancreatectomies*

Complication	N	Deaths (N)
Bronchopneumonia	7	1
Pleural effusion	4	—
Myocardial infarction	1	1
Hepatic insufficiency	13	—
Venous catheter sepsis	1	1
Total	26	3

Surgical Complications

There were 66 surgical complications, two thirds of which required reoperation. The list (Table 4) is headed both in number and severity by complications at or around the pancreatic anastomosis, followed by bleeding problems and biliary leaks. Abscesses and some more esoteric complications: chylous ascites, perforation, and jejunal torsion, conclude this list, which now will be discussed in detail.

Complications Concerning the Pancreatic Anastomosis

The group of complications feared most is that concerned with the pancreatic remnant or its anastomosis after the Whipple operation. In 233 anastomoses there were 25 complications (11%) and one fifth of these were fatal (Table 5). There was a manifest leak in 11 cases. However, with the abdomen open at relaparotomy it is not always easy to distinguish this from severe pancreatitis in the pancreatic remnant. Such an acute postoperative pancreatitis occurred 11 times.

Three bland pancreatic fistulae closed spontaneously after 2–3 weeks. The experience from two American centers (the Lahey and Mayo Clinics) with this complication are very similar: in a total of 403 Whipple procedures there were 34 pancreatic leaks (8%) with 9 fatalities (26%).[8,9]

Diagnosis. The key to successful treatment of these complications is early diagnosis. The simple clinical

TABLE 4. *Surgical Complications, Relaparotomy, and Mortality Rates after 285 Pancreatectomies*

Complication	N	Relaparotomy	Mortality
Pancreatic leak	25	17	5
Abdominal pain	2	2	—
Bleeding			
Gastrointestinal	12	8	1
Operating field	4	4	—
Bile fistula	8	5	—
Abscess			
Hepatic	5	2	—
Abdominal	2	2	—
Chylous ascites	6	—	—
Gastric perforation	1	1	—
Jejunal torsion	1	1	—
Total	66	42	6

findings elicited by continuous observation on the surgical intensive care unit that provide first clues are: a beginning abdominal tenderness where there was none before; the tongue slightly drier than usual; a rise in temperature, pulse or respiratory rate; oliguria and a barely perceptible agitation. Laboratory findings (leukocyte count, serum amylase, creatinine levels, etc.) invariably lag behind these subtle clinical signs. The same applies to modern imaging procedures including ultrasound and CT scans performed routinely 1 week after operation.

Case 1

A 58-year-old adipose and jaundiced patient had a Whipple procedure performed for a papillary carcinoma. Ten days later he was restless and had a slight rise in temperature and beginning epigastric rigidity. The CT scan showed an edematous pancreas and ultrasound confirmed the presence of subfascial fluid collection (Fig. 1). It was tempting just to aspirate this percutaneously. However, the clinical signs indicated something deeper and more serious, and relying on them we found a small anastomotic leak with severe pancreatitis. Removal of the remaining pancreas (total pancreatectomy) led to the recovery of this patient.

Case 2

A 60-year-old man had a palliative biliary bypass (choledochoduodenostomy) performed elsewhere for obstructive jaundice due to carcinoma of the pancreatic head. Four weeks later we performed a Whipple procedure (including portal vein resection with a mesentericocaval anastomosis). On the second postoperative day, he had tachycardia, a dry tongue, and epigastric tenderness. The tube placed to splint the biliary anastomosis then began to drain blood. At laparotomy the pancreatic anastomosis was intact. However, the jejunal loop draining it was distended and the pancreatic remnant had the mottled appearance of pancreatitis (Fig. 2). The explanation for this complication was a spurting bleeder, which we found on the cut surface of the pancreas. Due to a kink in the draining jejunal loop and a large obturating blood clot in that same loop, the blood had no free run-off. The resulting back pressure probably induced the pancreatitis. Again, the solution was a total pancreatectomy and the patient recovered.

TABLE 5. *Complications Occurring at or around 233 Pancreatojejunostomies*

Complication	N	No. of Deaths
Anastomotic leak	11	4
Acute pancreatitis	11	1
Pancreatic fistula	3	—
Total	25	5

In cases with a Völker drain splinting the biliary anastomosis, a leak may be demonstrated directly by injecting contrast medium into this drainage tube with the patient lying on his left side. But here again, it is the clinical signs rather than the radiologic findings of a leak that favor reintervention.

Case 3

A 47-year-old man had a Whipple operation for a distal common duct carcinoma. One week later a routine x-ray with contrast medium

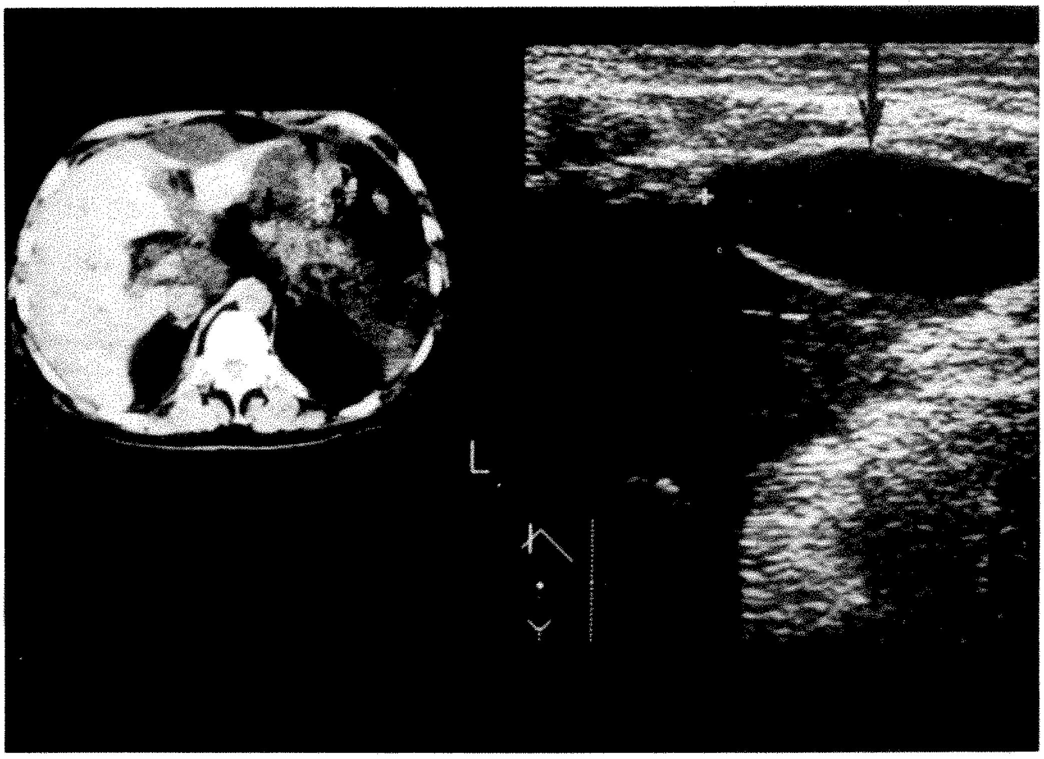

FIG. 1. *Left.* CT 10 days after Whipple procedure. Arrows point at edematous pancreatic remnant. *Right.* Ultrasound of same patient demonstrates subfascial fluid collection.

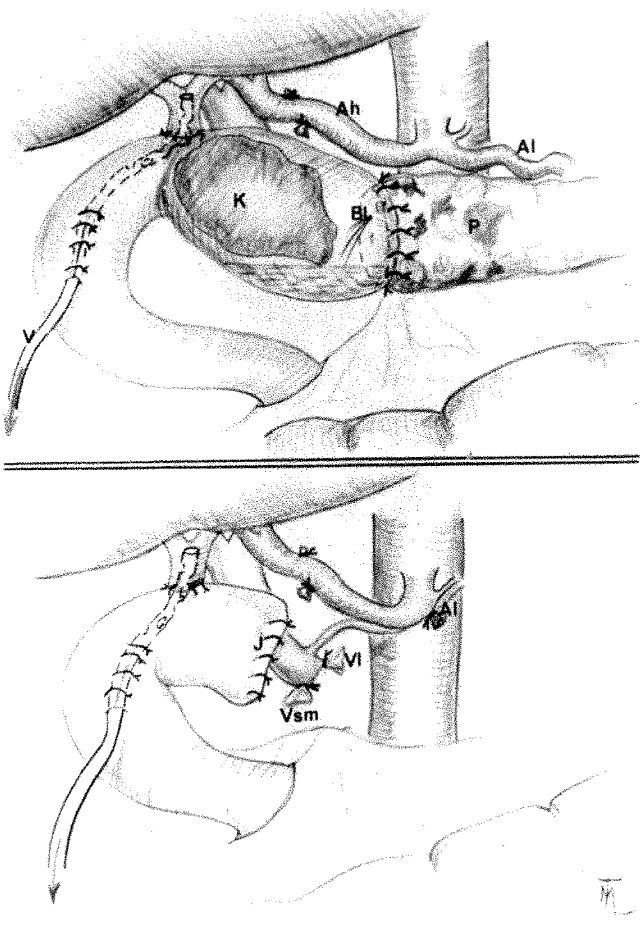

FIG. 2. *Top.* Diagram showing site of operation 2 days after Whipple procedure. Ah = hepatic artery; Al = splenic artery; V = Völker drain; K = blood clot; BL = bleeding from cut surface of pancreas; P = pancreatic remnant with pancreatitis. *Bottom.* Diagram after removal of remaining pancreas. J = jejunal stump oversewn; Al = splenic artery; Vl = splenic vein. The superior mesenteric vein (V.s.m.) had been anastomosed to the inferior vena cava at the first operation.

injected *via* the transjejunal tube splinting the biliary anastomosis showed a leak at the pancreaticojejunostomy (Fig. 3). The normal clinical state of this patient permitted expectant treatment, and further control x-rays demonstrated spontaneous closure of this fistula without any intervention.

Treatment. Table 6 summarizes our treatment for these 25 pancreatic complications. In eight cases treatment was entirely conservative. This group includes three patients with a radiologically proven fistula. However, in these patients the clinical course was bland and spontaneous closure of the leaks followed in 2–3 weeks (Fig. 3).

In five of 11 patients the diagnosis of postoperative acute pancreatitis rested mainly on laboratory tests (*i.e.*, rise in serum amylase level). The first of these (in fact the first complication in this series) was misjudged by us: the patient died 11 days after pancreaticoduodenectomy before it became clear that her acute respiratory distress syndrome was secondary to acute pancreatitis. This experience led us to follow the rule of early reintervention when in doubt. As a consequence, two patients were reoperated on for unusual postoperative pain, who then proved to have intact anastomoses and no abdominal pathology at all. At least these "unnecessary" relaparotomies did no harm.

In a group of five patients, treatment was confined to lavage and drainage. Twice the leak had not yet led to any significant peritonitis or pancreatitis. These were both successfully treated by a combination of measures (Fig. 4): the pancreatic duct was occluded with Ethibloc and sutured, the jejunum was oversewn, and an irrigation and suction tube was placed to drain the pancreatic stump.

The very poor condition of three patients did not permit anything more than renewed drainage to be done. Only one of these patients survived.

There were 12 patients in whom the radical solution, namely total pancreatectomy, seemed unavoidable. Two patients died of uncontrollable erosive hemorrhage. However, in 10 of 12 patients, total removal of the remaining pancreas was life-saving.

Prevention. There have been many ingenious suggestions for the prevention of these complications at or around the pancreatic anastomosis. So far there only has been one certain prophylaxis: that is to avoid it altogether by doing a total pancreatectomy whenever the pancreatic remnant is very friable and the duct narrow.[10]

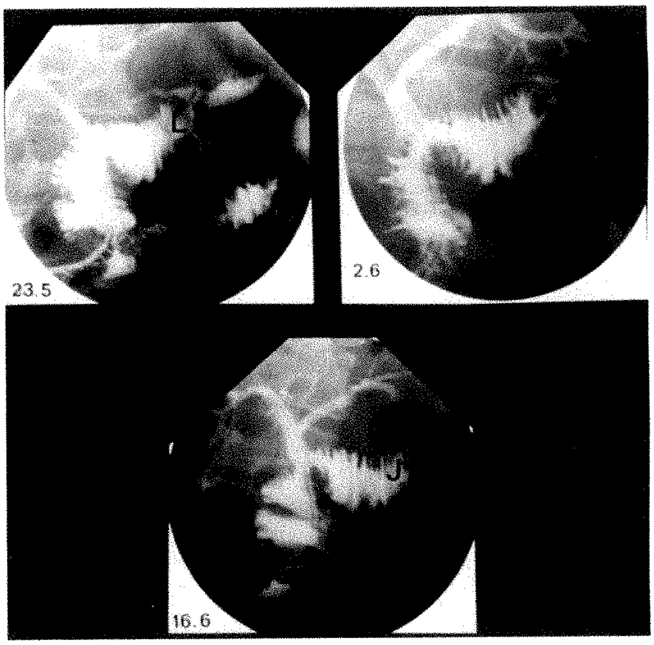

FIG. 3. X-ray with contrast medium injected through tube splinting the hepaticojejunostomy. L = leak of contrast medium through the pancreaticojejunostomy; J = the anastomosis has healed 24 days later.

TABLE 6. *Treatment of 25 Postoperative Pancreatic Complications*

		Treatment			
Complication	N	Conservative	Drainage	Total Pancreatectomy	No. of Deaths
Anastomotic leak	11	—	5 (2 deaths)	6 (2 deaths)	4
Acute pancreatitis	11	5 (1 death)	—	6	1
Pancreatic fistula	3	3	—	—	—
Total	25	8 (1 death)	5	12 (2 deaths)	5

All variations of the standard end-to-end telescope pancreaticojejunostomy have not produced better results. It does not seem to matter if additional cover is given by jejunoplication,[11] whether the pancreas is buried within the stomach wall,[12] whether three separate loops of gut are used for the gastric, biliary, and pancreatic anastomoses,[13] and whether the pancreatic duct is drained,[14] ligated, occluded, or oversewn, or all three.[15] Even doing nothing to the pancreatic remnant except for leaving a drain in its vicinity has been attempted.[16] That leaves us with the truism that in the end only a meticulous and standardized technique will lower the rate of this complication. And, once it has occurred, only its speedy detection and treatment by early reintervention can save the patient.

Postoperative Hemorrhage

Postoperative bleeding was the second common complication occurring in 16 patients (5.6%), requiring relaparotomy in 12 and ending fatally in one (Table 7).

Hemorrhage arose within the gastrointestinal tract in 12 cases, mostly from the gastroenterostomy and never from an acute stress ulcer. The presence of a day-and-night endoscopy service is invaluable here. Immediate gastroscopy can locate the site of bleeding and was successful in stopping it by laser or injection therapy in four cases.

In all but one of the remaining eight patients, relaparotomy and an additional suture stopped the bleeding. This fatality was partly due to our too-conservative approach: the oozing from the gastrojejunal suture line did not appear to be serious and endoscopic therapy was successful at first; the patient rebled, aspirated, and relaparotomy came too late. Four patients (not counting those with anastomotic leaks) bled from one of the large retroperitoneal vessels. In each patient, timely relaparotomy and suture successfully stopped the hemorrhage.

Case 4

A 61-year-old adipose and jaundiced man had a Whipple resection performed for pancreatic carcinoma. Ten days later, total pancreatectomy was done because of a acute pancreatitis in the remnant. He recovered from both operations and was discharged home three weeks later. However, he was readmitted 6 days later with pyrexia and repeated vomiting of small amounts of blood. The endoscopist located the site of the bleeding by threading the endoscope into the proximal jejunal loop; a trickle of blood was seen clearly coming from the sutured jejunal stump (Fig. 5, *top*).

At laparotomy we found a pulsating false aneurysm at this point, possibly emanating from the eroded stump of the splenic artery (Fig. 5, *bottom*). High clamping of the aorta, exposure of the aneurysm, and suture of the leak stopped the bleeding, and the patient was discharged 12 days later.

In the American experience (Lahey and Mayo Clinics) there were a total of 54 hemorrhagic complications after 403 pancreaticoduodenectomies (13%) in which 27 ended fatally.[8,9] Routine stress ulcer prophylaxis, prompt endoscopic diagnosis, and early revision, if necessary, can save most of these patients.

The role of vagotomy in the prevention of bleeding in patients who have a pancreatectomy is controversial. The ulcerogenic potential of partial or total pancreatectomy has prompted some clinics to recommend prophylactic truncal vagotomy for all of these patients.[17,18] In our experience anastomotic ulcers have not been a problem even on late follow-up, and a prophylactic va-

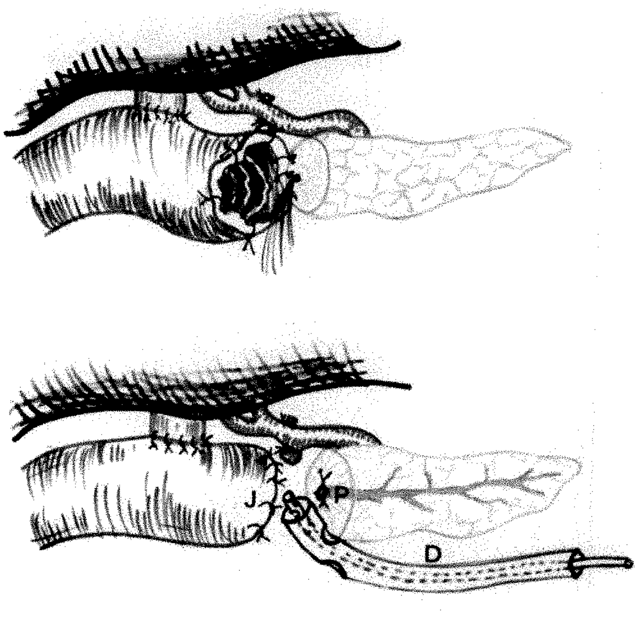

FIG. 4. *Top.* Breakdown of pancreaticojejunostomy after Whipple procedure. *Bottom.* Repair by occlusion of pancreatic duct (P) with Ethibloc, closure of jejunal stump (J), and irrigation-suction drain (D).

TABLE 7. *Hemorrhagic Complications, Relaparotomy, and Mortality Rate after 285 Pancreatectomies*

Site of Hemorrhage	N	Relaparotomy	Mortality
Gastrointestinal	12	8	1
Operative field	4	4	—
Total	16	12	1

gotomy is unlikely to influence bleeding problems in the early postoperative period.[19,20]

TABLE 8. *Biliary Leakage and its Treatment after 285 Pancreatectomies*

		Therapy			
Site of Leak	N	Conservative	Operative Drain	Suture	Mortality
Hepaticojejunostomy	4	2	2	—	—
Biliary drainage	2	—	2	—	—
Accessory bile duct	2	1	—	1	—
Total	8	3	4	1	0

Biliary Fistula

Biliary leaks after partial or total pancreatectomy are rare and relatively harmless in our experience (Table 8). We came across eight such instances of 285 patients at risk (3%) and all survived. The Lahey and Mayo Clinics reported on 46 biliary fistulae with four deaths after 441 pancreatectomies.[8,9]

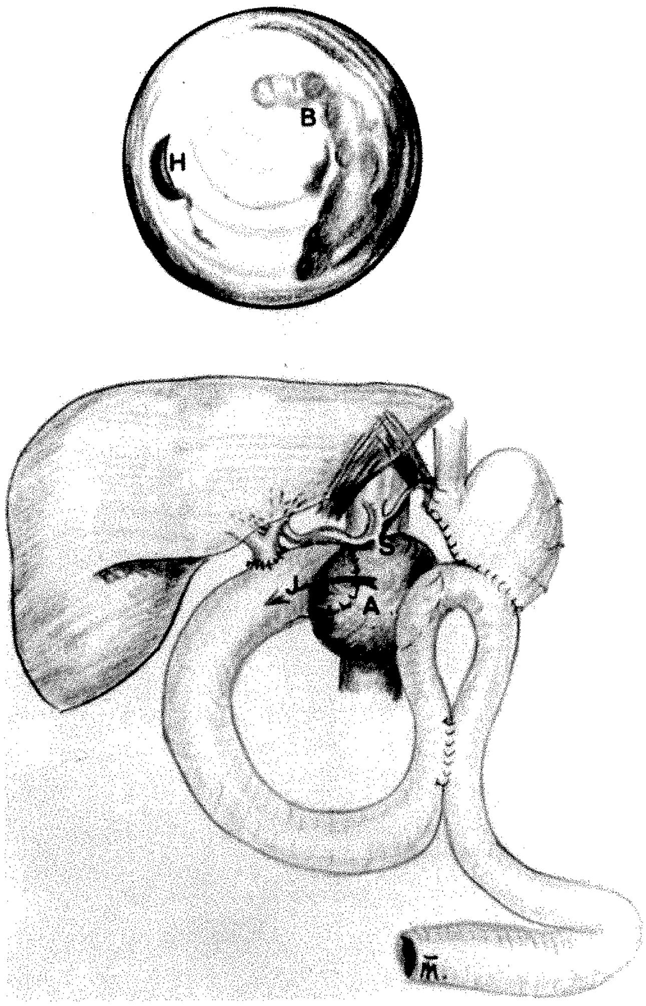

FIG. 5. *Top.* Diagram of endoscopic view into the proximal jejunal stump following total pancreatectomy. H = opening of hepaticojejunostomy draining bile; B = blood clot and fresh blood entering the jejunal stump. *Bottom.* Diagram of situation following total pancreatectomy with false aneurysm (A), arising from ligated splenic artery (S), and penetrating into the jejunal stump (J).

True anastomotic leaks occurred in four cases, two of which required renewed drainage. The other two fistulae sealed off spontaneously. Twice the bile leaked due to dislocation of the Völker drainage tube, used to splint the biliary anastomosis (Fig. 6). Removal of this drain solved the problem. Currently we use such splints only if the bile duct is narrow (less than 10 mm in diameter).

Leakage from an accessory bile duct, overlooked at the first operation, required a new anastomosis in one case only.

Miscellaneous Complications

Abscess. Seven genuine abscesses either hepatic or intra-abdominal were readily located by means of ultrasound or CT (Fig. 7). Percutaneous drainage under ultrasound guidance was possible in three of these cases; the remainder required operative drainage (Table 4).

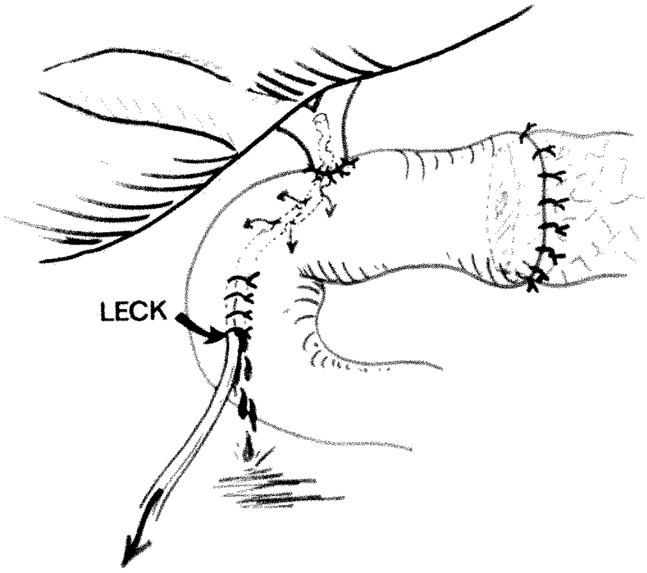

FIG. 6. Diagram demonstrating leakage of bile from the site of exit of the Völker drain.

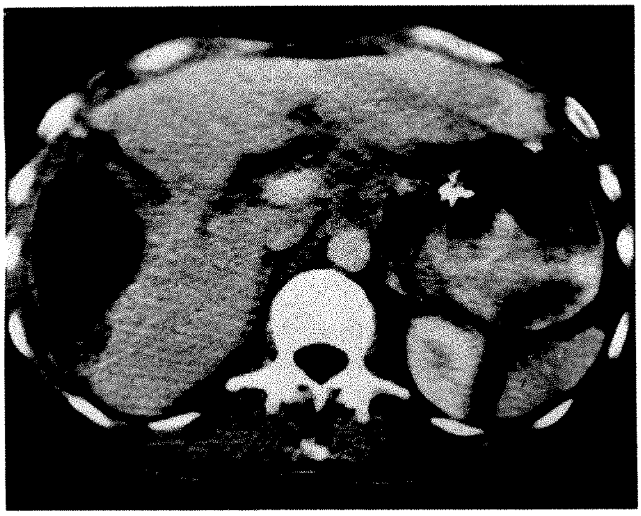

FIG. 7. CT demonstrating hepatic abscess after a Whipple procedure.

Chylous ascites. Chylous ascites occurs relatively rarely considering the extensive lymph node dissection that occurs with every pancreatectomy for cancer.[21] It can reach alarming proportions of several liters per day even requiring parenteral nutritional support. In each of our 6 cases secretion ceased spontaneously within 1 or 2 weeks.

Gastrointestinal fistula. Leakage of the gastrojejunal anastomosis, reported to occur in around 2% of cases,[8] was not seen in this series. However, one gastric perforation occurred high on the greater curvature of the stomach 7 days after total pancreatectomy with splenectomy. The cause was a small area of necrosis following ligature of the short gastric vessels. After this experience, we always secure the greater curvature with a row of Lembert sutures after total pancreatectomy.

Gastrointestinal necrosis. The following case report describes this curious complication.

Case 5

A 57-year-old jaundiced man had a carcinoma of the pancreatic head removed by a Whipple operation. After an uneventful course he had a fever, brief epigastric pain, and dyspnea on the seventh postoperative day. Since the patient seemed to improve spontaneously, we were inclined to blame this brief episode on a mild basal pneumonia, particularly since a chest x-ray seemed to confirm this.

On the next day a routine CT control showed some curiously dilated loops of bowel in the upper abdomen (Fig. 8). When the patient had another spike of temperature (39 C), we decided to reoperate. The proximal jejunal loop draining the pancreatic remnant and bile duct was grotesquely dilated and ischemic due to torsion at the Braun jejunostomy. Again there was no choice but to convert the Whipple into a total pancreatectomy and to bring up the next loop of jejunum for a new biliary anastomosis (Fig. 9).

This case emphasized once more that postoperative respiratory distress only rarely is primarily of pulmonary origin (even if x-ray evidence seems to support this

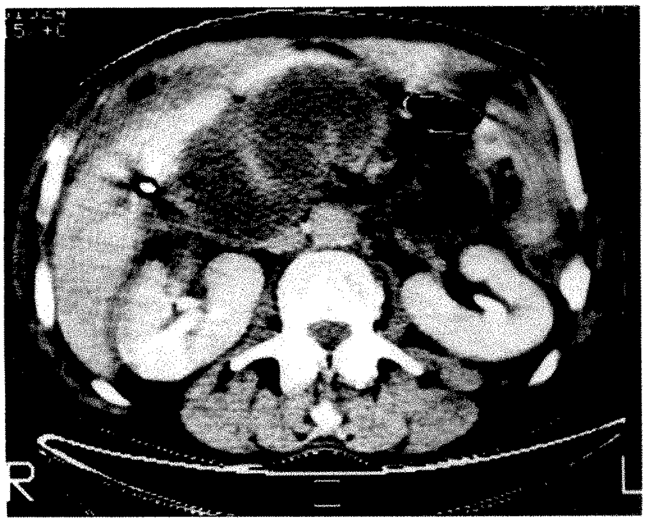

FIG. 8. CT 8 days after a Whipple procedure showing dilated, edematous jejunal loop in the immediate subhepatic space.

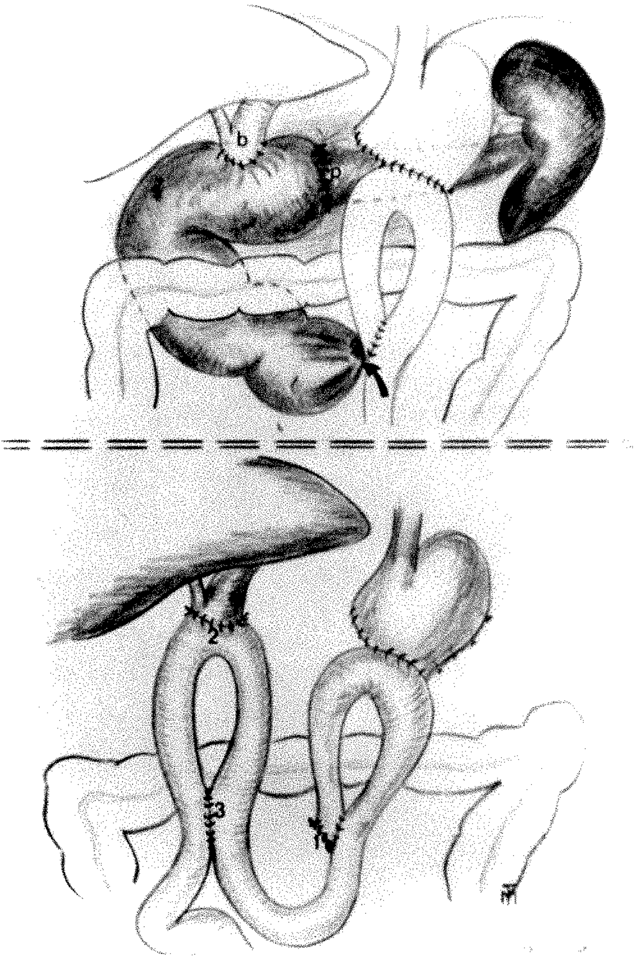

FIG. 9. *Top.* Diagram of operative site after a Whipple pancreatectomy. Arrow points to torsion of the proximal jejunal loop at the Braun jejunojejunostomy. b = hepaticojejunostomy; p = pancreaticojejunostomy. *Bottom.* Operative site after the removal of the offending jejunal loop, remaining pancreas, and spleen. 1 = oversewn jejunum at site of Braun anastomosis; 2 = new hepaticojejunostomy; 3 = new jejunojejunostomy.

TABLE 9. *Influence of Preoperative Obstructive Jaundice on the Occurrence and Mortality of Postoperative Pancreatic Leaks and Bleeding Problems in 41 Patients*

	With Jaundice		Without Jaundice	
Complication	N	No. of Deaths	N	No. of Deaths
Pancreatic leak	23	4	2	1
Postoperative bleeding	12	1	4	0
Total	35	5	6	1

view). The real cause lies below the diaphragm in the operative field.

Discussion

On analysing these 92 complications after 285 pancreatectomies, one begins by looking for risk factors that might have caused them. Of all the nonsurgical factors studied (age, preoperative nutritional state, weight loss, etc.) only jaundice was of significance.

Of the 41 patients who had the two most prevalent and serious complications, a pancreatic leak or hemorrhage, 35 (85%) had obstructive jaundice before operation (Table 9). Five of the six deaths that occurred after these two major complications occurred in jaundiced patients. Is it worthwhile then to relieve this obstructive jaundice before operation? Three recent prospective trials addressed to this problem seem to show that this is not so.[22-24] The results summarized in Table 10 show that neither morbidity nor mortality were lowered by preoperative biliary drainage; in fact, this drainage had a morbidity of its own. However, in all three trials, drainage was performed by the rather unsatisfactory percutaneous transhepatic route. Furthermore, the bile was drained to the outside instead of into the gut where it belongs.

TABLE 10. *The Value of Preoperative Biliary Drainage (PTD) on Postoperative Morbidity and Mortality as Studied in Three Prospective Trials*

	Morbidity		Mortality	
First Author	With PTD	Without PTD	With PTD	Without PTD
Hatfield (1982)[22]	14%	15%	14%	15%
McPherson (1984)[23]	33%	42%	32%	19%
Pitt (1985)[24]	46%	53%	8%	5%

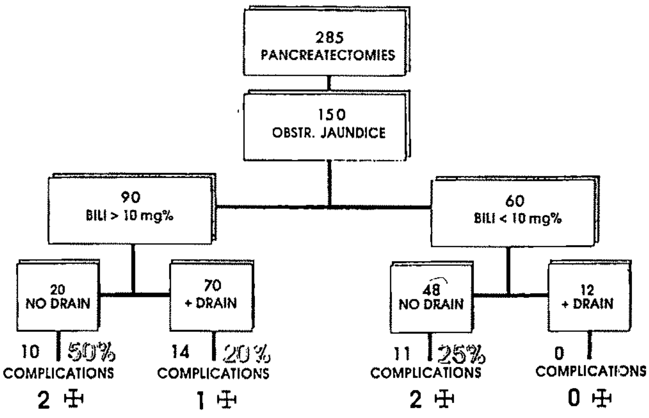

FIG. 10. Morbidity and mortality after pancreatectomy (partial and total) in a 150 patients with obstructive jaundice. Irrespective of the severity of jaundice (90 patients with bilirubin levels above, and 60 with bilirubin levels below 10 mg%), those drained before operation had less postoperative morbidity and mortality.

The analysis of our own jaundiced patients who had pancreatectomy seems to show a favorable effect of drainage by endoscopic transpapillary intubation, *i.e.*, into the duodenum (Fig. 10). There is no doubt that those patients who had drainage before operation did much better regarding complications and mortality irrespective of the severity of the obstructive jaundice.[25] However, this study was retrospective and not randomized. Perhaps the discrepancy between the results as shown in Table 10 can be explained by the different methods of biliary drainage used and by the fact that in obstructive jaundice the recovery of hepatic functions depends on many factors: the intensity and preoperative duration of jaundice and the length of the decompression. As Koyama and co-workers showed, it takes at least 4–6 weeks of decompression before hepatic mitochondrial functions return to normal.[26] This is probably longer than is feasible in cancer patients. For these reasons, we believe that the discussion on this question of preoperative decompression is not yet closed. Until it is, we will drain all jaundiced patients, if this can be done easily, at the time of the initial endoscopic cholangiography.[27] We have in so far revised our position, which used to favor one-stage pancreatectomy even in severely jaundiced patients.[25]

An additional risk factor possibly responsible for impaired healing of the pancreatic anastomosis is ischemia due to celiac artery occlusion.[28] With routine preoperative angiography one encounters few cases with such an occlusion and perfusion of the hepatic and splenic arteries *via* pancreatoduodenal arcades. The unavoidable division of these vessels during a Whipple procedure could theoretically cause ischemia of the pancreatic remnant. In actual practice this danger is overrated since other collaterals probably come in. None of our patients with surgical complications had evidence of celiac occlusion on routine preoperative angiography. Conversely, in our six patients with such a vascular obstruction, occlusion of the gastroduodenal artery did not measurably reduce flow in the hepatic artery nor were there any postoperative complications.

One final risk that deserves mention is the surgeon himself. It seems axiomatic that formidable operations such as partial and total pancreatectomy should be concentrated in those centers where experience can keep complications to a minimum or at least deal with them successfully should they occur.[29,30,31] Such centers all over the world are now reporting large pancreatectomy series with low morbidity and mortality rates under 5%.[11,32,33] However, the pioneer days of pancreatectomy are over, and towards the end of this century the well-trained "occasional pancreatectomist" may produce equally good results,[34] provided that he adheres to the following rules: (1) optimal preoperative preparation of the patient, including neutralization of the deleterious effects of obstructive jaundice and malnutrition as far as possible; (2) meticulous attention to detail in the performance of the operation itself; and (3) continuous, close observation of the patient in the postoperative period so as to detect complications on time.

Acknowledgments

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Operative Treatment of Crohn's Ileocolitis Complicated by Ileosigmoid and Ileovesical Fistulae

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Ileovesical and ileosigmoid fistulae were found to coexist in 22 patients with Crohn's ileocolitis. Persistent or recurrent urinary tract infection was a complaint in all cases, and 11 patients reported pneumaturia and/or fecaluria. Thus, bladder involvement was either suspected or clinically apparent in each patient. The cystogram was the best confirmatory test for the ileovesical fistula (positive in 9 of 22 patients). The coexistence of the sigmoid fistula was best diagnosed on intestinal radiographs (positive in 9 of 22 patients); there were no clinical signs of its presence. The coexistence of ileosigmoid and ileovesical fistulae was the sole indication for operation in two patients. In all others, a combination of factors required surgical therapy. An ileocolonic resection with primary intestinal anastomosis was performed in 16 patients and exteriorization was performed in six patients. The sigmoid defect was closed primarily in 16 patients and required wedge resection in the other six patients. The bladder defect was sparingly excised and closed with absorbable sutures. All patients recuperated without anastomotic leaks, bladder leaks, or persistent cystitis. This experience indicates that coexisting ileosigmoid and ileovesical fistulae may add complexity to an ileocolonic resection for Crohn's disease, but is not a difficult management problem for the gastrointestinal surgeon.

INTERNAL FISTULAE extending from the diseased intestine into any of the intra-abdominal or retroperitoneal organs and structures occur in approximately 40% of patients with ileocolonic Crohn's disease.[1,2] Usually, the development of these fistulae signals exacerbation or progression of the inflammatory process and is associated with the formation of a phlegmon or abscess, which becomes clinically evident as generalized malaise, tender abdominal masses, and the symptoms and signs of a small bowel obstruction. Often, this course is not abated completely by aggressive medical management, and surgical treatment becomes necessary. An ileovesical fistula that complicates the clinical course is found in 2–5% of patients who have operative treatment for Crohn's ileocolitis.[2–6] A concurrent ileosigmoid fistula may further complicate the clinical situation.[1,7,8]

An ileovesical fistula alone is often considered to present an urgent and sometimes difficult management problem for the gastrointestinal surgeon.[4,5] If an ileosigmoid fistula is also present, the combined problems may require special surgical expertise.

Patients

We describe our experience over the past 15 years with 22 patients who were diagnosed as having fistulous communications between the diseased ileum, the urinary bladder, and the sigmoid colon. Of these 22 patients, 15 were male and seven were female; their ages ranged from 13 to 54 years, with an average of 29 years. They had been diagnosed as having Crohn's disease from 1 to 25 years previously, with an average of 7 years. Six of the patients had undergone previous surgery related to Crohn's disease: four had had laparotomies without intestinal resections, which led to the diagnosis of the disease, and two had had ileocolonic resections. During the same time interval (15 years), we treated surgically 39 patients with an ileovesical fistula alone and 68 patients with an ileosigmoid fistula alone, both associated with Crohn's disease.

Clinical Features

All 22 patients had the ileocolonic form of Crohn's disease, with varying degrees of involvement of the ileum and colorectum; all patients had an exacerbation of their disease shortly before or coinciding with the development of the fistulae, and all had urinary tract infections. In five patients, the infection was accompanied by both pneumaturia and fecaluria, two others had

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only pneumaturia, and four patients had only fecaluria. Ten patients also had a tender abdominal mass, which was associated with an intra-abdominal abscess in six patients. Seven patients had recurrent episodes of small bowel obstruction, and in 12 patients, the major concern was debility due to weight loss and pain not alleviated by aggressive medical treatment. All patients complained of bouts of diarrhea and defecatory frequency; however, these symptoms were not prevalent in those patients who were later found to have a large fistulous communication to the sigmoid colon.

Before operation, all patients received standard medical management (dietary restriction, steroids, Azulfidine®). Various antibiotics were given before operation for treatment of a urinary tract infection. Nine patients received total parenteral nutrition (TPN) and bowel rest before surgery, for 2 weeks to 6 months, for correction of malnutrition caused by the disease. Although TPN improved their condition, it did not result in closure of the fistulae.

Preoperative Evaluation

Cystography, performed in conjunction with an intravenous pyelogram on all 22 patients, indicated a vesical fistula in nine patients; in three of these patients, a fistulous tract was evident from leakage of contrast medium into an adjacent intestinal loop, and in the other six patients, either a mass defect or irregularities at the dome of the bladder were noted (Fig. 1). Eight of the 11 patients with pneumaturia and/or fecaluria had normal cystograms.

Cytoscopy was performed on 10 patients. A fistula was identified in six patients and severe generalized cystitis in one patient; inflammatory changes were seen at the dome of the bladder in the remaining three patients, suggesting the presence of an enterovesical fistula. Three patients with pneumaturia/fecaluria did not have cystoscopy, and three of those with positive findings on cystoscopy had neither pneumaturia nor fecaluria.

Both gastrointestinal radiography and proctosigmoidoscopy were performed on all 22 patients. The ileovesical fistula was detected by barium leakage into the bladder during a small bowel contrast study in only two patients. The ileosigmoid fistula was identified by barium contrast in nine patients (Fig. 2) and during proctosigmoidoscopy in three patients. In only one patient was the ileosigmoid fistula diagnosed by both tests.

Operative Treatment

The presence of an ileovesical fistula was the sole indication for operation in only two patients who had severe unrelenting cystitis. In the remaining 20 patients, laparotomy was performed because of complicating factors that coexisted with the fistulae; these included a tender abdominal mass that was unresponsive to medical management (10 patients), an abscess (6 patients), recurring small bowel obstruction (7 patients), and failure of medical treatment with steroids, antibiotics, and bowel rest (12 patients).

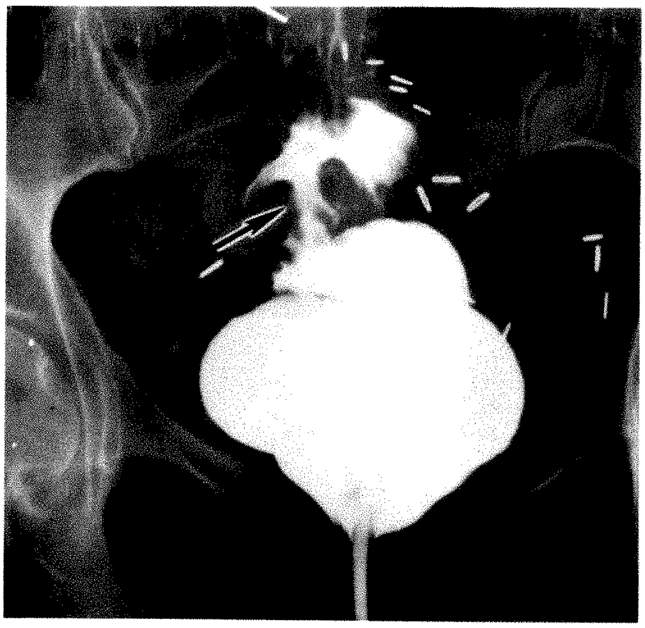

FIG. 1. The cystogram demonstrates a mass defect, mucosal irregularity, and a large fistula at the dome. The irregularity reflects mucosal inflammation and, in the presence of Crohn's disease, indicates the presence of an enterovesical fistula, even if an obvious communication with the bowel is not seen.

All patients underwent ileocolonic resection. A primary ileocolonic anastomosis was performed in 16 pa-

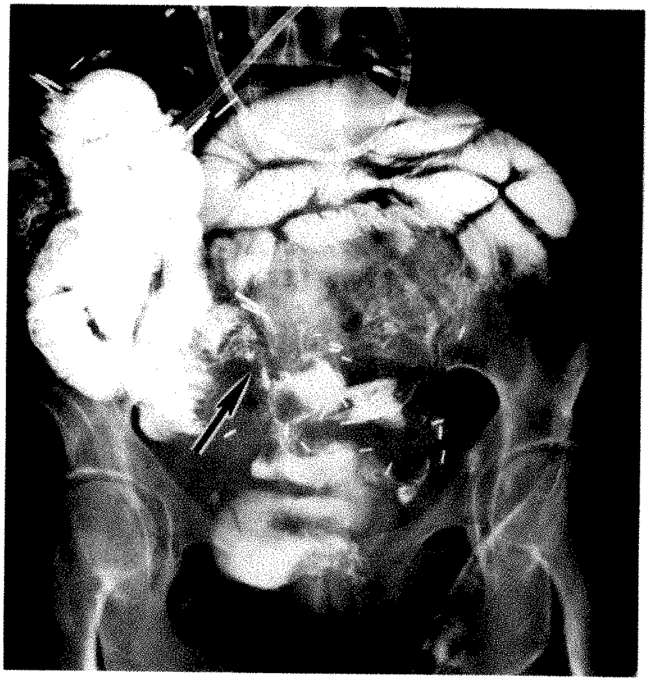

FIG. 2. The small bowel radiographic study demonstrates early sigmoid-rectal filling indicating the presence of an ileosigmoid fistula.

tients and exteriorization was performed in six patients (ileostomy, 5 patients; transverse-loop colostomy, 1 patient) who had a large intra-abdominal abscess (4 patients) and/or severe disease in the distal colon (2 patients).

In each patient, there was a single fistulous opening in the bladder that was in communication with the diseased ileum, either directly or through an abscess cavity, also giving rise to the sigmoid fistula. None of the patients had a direct sigmoid-vesical fistula separate from the ileal communication. In each patient, the dissection of the coexistent ileovesical and ileosigmoid fistulae was carried out in part bluntly by finger fracture for separation of the edematous, phlegmonous ileal and sigmoid mesentery and peritoneum at the dome of the bladder, and in part sharply for division of the actual fibrotic fistulous tracts. The bladder defect was excised sparingly or debrided and was closed with absorbable sutures; a urethral catheter was placed and remained for 1 week. The sigmoid defect was excised and closed by direct suture in 16 patients. The other six patients required a sigmoid wedge resection because they had multiple defects associated with stricture formation. The wound was closed primarily in 13 patients; delayed closure was the preferred method for the other nine patients.

Results

None of the patients had an intestinal anastomotic leak, a bladder leak, or persistent cystitis. The urine cleared within 2 days in 20 patients and within 7 days in the remaining two patients. A postoperative cystogram demonstrated that the bladder closure was intact in all patients tested.

Three patients had postoperative complications: a brachial vein thrombosis occurred in one patient, but did not require operative treatment; in another patient, an ileus developed, which resolved spontaneously; and the third patient had an intra-abdominal abscess that required operative drainage. The abscess was encountered at the dome of the bladder and extended to the left paracolic gutter. The patient had an uneventful recovery after the drainage.

Follow-up times ranged from 1 to 13 years. Crohn's ileocolitis recurred in six patients and an ileovesical fistula recurred in 1 of these 8 years after the initial resection.

Discussion

Our experience in the operative treatment of Crohn's ileocolitis includes surgery on 68 patients with an ileosigmoid[8] and 39 patients with an ileovesical fistula.[6] The review of this experience demonstrated that, if patients with Crohn's disease have an ileovesical fistula, there is a 60% probability of a concomitant sigmoid communication, and that patients with an ileosigmoid fistula have a 30% likelihood of also harboring a urinary bladder fistula. The high frequency of coexistence of these two types of fistulae in the presence of Crohn's disease must lead one to anticipate an ileosigmoid fistula once a communication with the urinary bladder is diagnosed, and *vice versa.*

An enterovesical fistula is discovered most readily on the basis of clinical findings. Dysuria was present in all of our patients, and pneumaturia and/or fecaluria was reported by 11 of the 22 patients (50%). The cystogram is the most helpful confirmatory diagnostic test. We noted that cystoscopy and intestinal radiography do not reliably indicate the presence of a vesical fistula. Such a fistula is almost always diagnosed before operation, and thus it is rarely an unsuspected intraoperative finding. An ileosigmoid fistula, however, which does not cause any specific clinical signs or symptoms, may not be detected until a laparotomy is performed. The coexistence of an ileosigmoid fistula was best diagnosed by radiographic examination, with a confirmation rate of 41% (9 of 22 patients). Conceivably, a very large ileosigmoid fistula could bypass the colon and cause rapid intestinal transit and severe diarrhea, thus indicating its presence clinically; however, diarrhea is the most common complaint of patients with Crohn's disease and certainly cannot be considered pathognomonic of an ileosigmoid fistula.

Given the frequent coexistence, one should anticipate, if not attempt to diagnose, a concomitant sigmoid communication in patients who have an ileovesical fistula. The surgeon should realize, however, that the surgical treatment of an unsuspected sigmoid fistula is not at all more demanding than that of a fistula detected before operation.

There is no specific preoperative preparation for the patient with a sigmoid fistula that would alter the intraoperative course of action or simplify the surgical procedure. Preoperative evaluation and preparation are the same for any patient undergoing an ileocolonic resection for Crohn's disease. The surgeon should determine whether the colorectum, specifically the sigmoid and rectum, is primarily involved by Crohn's disease; the presence or absence of such involvement is readily determined by proctosigmoidoscopy, which must be included routinely in the preoperative evaluation of any patient with Crohn's ileocolitis. An obvious fistulous opening often cannot be detected on proctoscopy. Frequently, however, there are localized inflammatory changes such as pseudopolyps, mucosal edema, and friability at the presumed fistula site, whereas the adjacent colonic mucosa appears normal and uninvolved.[8] In addition to endoscopic evaluation of the distal colon, radiographs of the colon and small bowel, which might demonstrate a sigmoid fistula, are necessary for diagnosis and delineation of the extent of intestinal involvement by Crohn's disease, so that a treatment program (medical management or surgical intervention) can be established for the patient.

There are no other preoperative maneuvers, tests, or treatments that would in any way influence the intraoperative approach to the repair of a sigmoid fistula or coexisting ileosigmoid and ileovesical fistulae. The major advantage in anticipating a sigmoid fistula is that the patient can be informed more specifically as to the possibility of an additional sigmoid resection or suture repair of the sigmoid defect, and that he or she can be forwarned of a possible enterostoma if the sigmoid involvement is extensive.

Often, patients with Crohn's ileocolitis and an ileosigmoid communication can be managed well without operation. Nonoperative treatment has also been suggested for the patient with an ileovesical fistula who is not troubled by other complications requiring surgical therapy. It might be that some of our patients could have been managed without operation. However, none of our patients who were stable from a medical point of view (no sepsis, no obstructive symptoms) favored continued nonoperative treatment. In all patients, the symptoms of cystitis were so severe, if not intolerable, that definitive surgical therapy was strongly indicated.

In the patient with coexisting ileosigmoid and ileovesical fistulae, one would expect that colonic as well as ileal contents will pass into the bladder. This introduction of a considerably increased quantity of bacteria into the bladder could result in increasingly severe cystitis. Consequently, early surgical intervention is indicated in the presence of a sigmoid fistula in addition to an ileovesical fistula, whereas the presence of an ileovesical fistula without sigmoid involvement and without resulting severe dysuria might not warrant instant, aggressive surgical therapy.

We found that the incidence of fecaluria and the (subjective) complaints of severe dysuria was the same for patients with an ileovesical fistula alone and patients with coexisting ileosigmoid and ileovesical fistulae. Each group included patients with severe, incapacitating dysuria and patients with lesser complaints. The degree of cystitis probably depends on the size of the communication between the bladder and gastrointestinal tract and on the degree of purulence, and not on the coexistence of a sigmoid fistula.

Conceivably, a patient who has both an ileovesical and an ileosigmoid fistula has a particularly aggressive form of Crohn's disease that favors early recurrence. Follow-up of our patients, however, has failed to indicate a higher or earlier incidence of clinically recurrent Crohn's disease. Forty-five per cent of our patients had recurrent disease, a rate similar to that reported by other centers.[9-11]

In regard to the intraoperative management of coexisting ileosigmoid and ileovesical fistulae, the surgeon may encounter difficulties in dealing with the inflammatory mass that consists of the ileocecum, the adjacent sigmoid colon, and the markedly thickened and edematous mesentery, and is attached to the urinary bladder and the retroperitoneum. This mass must be separated diligently from the retroperitoneum, but can be sharply and bluntly dissected from the bladder. The bladder defect is debrided and simply closed with absorbable sutures. Unless there is extensive involvement, the sigmoid defect can be repaired in a similar fashion; otherwise, partial resection is required. The mesentery, which is often thickened and highly vascularized and contains edematous, enlarged lymph nodes, must be transected carefully. Decisions regarding primary intestinal anastomosis and wound closure are made on the usual basis of contamination, inflammation, condition of the bowel to be anastomosed, etc.,[8] *i.e.*, according to criteria that apply to any operation on the gastrointestinal tract.

In summary, coexisting ileosigmoid and ileovesical fistulae associated with Crohn's ileocolitis is a specific complication of Crohn's disease and requires definitive surgical treatment. The intraoperative management of the ileovesical fistula does not cause undue difficulties for the surgeon, since the bladder defect is always situated at the dome. The coexistence of a sigmoid communication adds complexity to the operation, but the surgeon can deal effectively and safely with this along with the vesical component by following established surgical guidelines and practices.

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Intraoperative and External Beam Irradiation for Locally Advanced Colorectal Cancer

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In view of poor local control rates obtained with standard treatment, intraoperative radiation (IORT) using electrons was combined with external beam irradiation and surgical resection, with or without 5-fluorouracil (5FU), in 51 patients with locally advanced colorectal cancer (recurrent, 36 patients; primary, 15 patients). Patients received 4500–5500 cGy (rad) of fractionated, multiple field external beam irradiation and an IORT dose of 1000–2000 cGy. Thirty of 51 patients (59%) are alive and 22 patients (43%) are free of disease. In 44 patients at risk ≥1 year, local progression within the IORT field has occurred in 1 of 44 (2%) and within the external beam field in 8 of 44 (18%). All local failures have occurred in patients with recurrence or with gross residual after partial resection, and the risk was less in patients who received 5FU during external irradiation (1 of 11, 9% *vs.* 6 of 31, 19%). The incidence of distant metastases is high in patients with recurrence, but subsequent peritoneal failures are infrequent. Acute and chronic tolerance have been acceptable, but peripheral nerve appears to be a dose-limiting structure. Randomized trials are needed to determine whether potential gains with IORT are real.

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EXTERNAL BEAM IRRADIATION has been combined with surgical resection, chemotherapy, and/or immunotherapy for locally advanced colorectal cancer (unresectable for cure due to tumor fixation, residual after resection, locally recurrent). In separate series from Princess Margaret Hospital[1] and the Mayo Clinic[2] using radiation alone or with immunotherapy, local recurrence was ≥90% in evaluable patients. When radiation, with or without 5-fluorouracil (5FU), is combined with surgery for primary lesions that are initially unresectable for cure or have residual disease remaining after subtotal resection, although local control is better than that seen with no resection, the risk of local recurrence still remains too high at 30–50%.[3]

In an attempt to decrease local recurrence and improve survival with an acceptable risk of complications, our institution initiated a prospective clinical trial combining intraoperative irradiation (IORT) using an electron beam with external irradiation and section, if feasible.[3] The intent of this paper is to present our experience with the combined approaches, including IORT, in a group of 51 patients with locally advanced colorectal cancer. Our results will be compared with those achieved in other IORT trials and with alternative treatment techniques.

Methods and Materials

Patient Group

From April 1981 to February 1986, 151 patients received IORT with electrons as a supplement to external beam irradiation with or without resection at our institution. Fifty-one patients had locally advanced adenocarcinoma of the colorectum (primary, 15; recurrent, 36). Disease category of the 51 patients at the time of presentation for irradiation is seen in Table 1. The site of initial colorectal lesion was the rectum in 39 patients (recurrent, 29), the sigmoid in six patients (recurrent, 3), and the extrapelvic colon in six patients (recurrent, 4).

General criteria for patient selection and preoperative evaluation have been detailed previously.[4–7] Patients

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with documented distant metastases are not usually candidates for IORT in our institution, since life span is not adequate to evaluate treatment-related effectiveness or toxicity. Two of the 51 patients in this series, however, had surgical resection of a solitary liver metastasis in conjunction with gross total or subtotal resection of their locally recurrent lesion.

Treatment Factors

The method of external beam radiation has been consistent in this group of patients. Doses of 4500–5500 cGy (rad)* were delivered in 180 cGy fractions, 5 days per week in 5–6 weeks. For pelvic lesions, treatments were given with linear accelerators using 10-mv photons and four field-shaped external beam techniques described previously.[8,9] With extrapelvic lesions, unresected or residual disease plus 5-cm margins of normal tissue were included to 4500 cGy with parallel opposed fields; reduced fields with 2–3 cm margins were treated to 5000–5500 cGy. As noted in Table 2, 49 of 51 patients (96%) completed all planned external irradiation. When used in conjunction with external irradiation, 5FU was given 500 mg/m^2 intravenous push for 3 consecutive days, week 1 and, if tolerable, week 5.

The sequence of surgery and external radiation is seen in Table 2. In the initial portion of the series, major resections were not performed after high-dose preoperative irradiation; therefore, patients had either low-dose preoperative irradiation (500 × 1, 2 patients; 1000/5 fractions, 2 patients; other, 1 patient) or none. Planned high-dose preoperative irradiation (5000–5500 cGy in 180 cGy fractions) was delivered before an attempt at surgical resection in 18 patients who had clinical disease fixation to unresectable structures that was confirmed by an abdominal pelvic CT. Subsequent gross total or subtotal resection was performed in four of four patients with primary presentation and in 13 of 14 patients with recurrence. The extent of resection before or after external irradiation and amount of residual disease by group is as follows: (1) primary: complete or gross total resection with microscopic residual [res(m)] in eight patients, partial resection with gross residual [res(g)] in seven patients; (2) recurrent: res(m) in 11 patients, res(g) in 23 patients, no resection in two patients.

Standard treatment is supplemental by IORT at the joint discretion of the surgeon and radiation oncologist. When high-dose preoperative irradiation precedes an attempt at resection, disease extent is reevaluated 3.5 to 4 weeks after completion of irradiation. If distant metastasis is not confirmed, resection is attempted in a hospital operating room. The radiation oncologist joins the surgeon at that procedure to help determine feasibility of a subsequent IORT boost and size and shape of the IORT cylinder. After abdominoperineal resection, optimal IORT field exposure is determined with regard to an abdominal *versus* perineal approach, and prone *versus* supine or lithotomy patient position.[6,7] If surgical exploration precedes external irradiation and residual or unresectable disease remains after an attempt at resection, a similar intraoperative assessment for IORT is performed.

TABLE 1. *Patient Group: Disease Category, Colorectal*

Disease Category	No. of Patients
Primary, resected-residual	11
Primary, unresectable for cure (disease fixation)	4*
Recurrent, resected-residual	21†
Recurrent, unresectable for cure	15*
Total	51

* Resected after planned high-dose preoperative RT 4 of 4 and 13 of 14 patients, an additional recurrent patient was not resected.

† Low-dose preoperative RT in 5 of 21 patients (see Table 2).

Patients selected for IORT have a secondary re-exploration in an operating room in the Radiation Oncology Department, preferably in 1–2 days, but occasionally as late as 10 days.[4] The area at risk is re-exposed and the patient is transferred within a sterile corridor to the linear accelerator room where the IORT boost is delivered.

The IORT dose is calculated at the 90% isodose line and is dependent on the amount of disease remaining after attempts at resection: res(m), 1000 cGy; res(g) ≤2 cm in largest dimension, 1500 cGy; unresected or res(g) >2 cm, 1750–2000 cGy. IORT characteristics are seen in Table 3. Electron energy varied from 9 to 18 MeV with the lower energies of 9 and 12 MeV used after gross total resection or with residual disease of minimal thickness. The 15 and 18 MeV energies and doses of

TABLE 2. *Treatment Characteristics: External Radiation with or without 5FU*

	N	%
Completed planned external irradiation	49	96
Method of Irradiation		
None or <500 rad	2*	4
After operation	26	51
Before and after operation†	5	10
Before operation‡	18	35
5FU during irradiation	16/49	33

* Both had surgery and IORT and full course external radiation was planned: one died 1 month after operation of sepsis; 1 had prolonged postoperative ileus.

† Before operation 500 × 1, 2; 1000/5, 2; 840/4, 1; after operation 4500–6000/180 rad fractions.

‡ 5040/28 fractions, 17; 2520/14 fractions, 1 (previous 4000 rad).

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* 1 cGy = 1 rad; 100 cGy = 1 Gray.

TABLE 3. *Treatment Characteristics: IORT*

	Primary	Recurrent
IORT energy and dose		
Electron energy (MeV)		
9	5	1
12	7	18
15	3	12
18	1	7
IORT Dose		
1000–1250	5	5
1500	5	11
1750	3	4
2000	3	17
2500	0	1*
Total fields/patients	16/15	38/36
Location of IORT Boost		
Extrapelvic		
Para-aortic or paravertebral	1	6
Postlateral abdominal wall	2	1
Other	1	1
Pelvic†		
Presacrum	4	19
Sidewall	7	21
Anterior	5	1

* Had previously received 4500 rad/25 fractions after resection of primary.

† Presacrum and pelvic sidewall could be within a single IORT field. Organ frequency within an IORT field: bladder in 7; ureter in 14; rectum in 1.

2000 cGy were used more commonly in patients with recurrent disease in whom gross residual more frequently existed after attempts at resection.

The size and shape of the lucite cylinders (cones) used for IORT are dependent on location of the IORT field. For all pelvic locations, circular cones with 15° or 30° bevels were used to conform to the anatomy of the presacrum, pelvic sidewall, or anterior pelvis. With the 30° bevel cones, the depth of the isodose curves is more shallow at the heel end of the cone than the toe end,[10] which may affect the placement of the treatment cone relative to the tumor bed or residual tumor. For extra pelvic lesions, rectangular and eliptical cones with flat or 20° bevel ends were most frequently used.

Fifty-five IORT fields were treated in 51 patients (abutting fields were used in 2 patients, and separate areas were treated in an additional 2). In three other patients, a shrinking-field technique was used to deliver 1000–1250 rad with a large cone to the area of gross total removal but narrow or microscopically positive margins, and a smaller cone was used to encompass an area of gross residual for an additional 500–1000 rad (total dose within second IORT field of 1750 in 1 patient, 2000 in 2 patients). Potential dose-limiting organs within an IORT field were the bladder in seven patients, the rectum in one patient, and the ureter in 14 patients. Nerve and vessel are usually within pelvic sidewall or presacral fields.

Results

Survival and Disease Status

Survival and disease status are shown in Table 4. Of the 15 patients who had primary disease, 10 (67%) are alive and eight (53%) are disease free (range: 10–64 months with 7 patients ≥15 months). One of five patients who died was disease free at autopsy. In the 36 patients who had recurrence, 20 (56%) are alive and 14 (39%) are free of disease progression (range: 8–50 months with 12 patients ≥12 months and 6 patients ≥2 years). One of 16 patients who died had no evidence of tumor progression. In two patients with disease progression, solitary liver metastases were resected before IORT.

TABLE 4. *Survival and Disease Status: Colorectal IORT*

		Alive		Dead	
Disease Category	No. of Patients at Risk	NED # (%)	Failure # (%)	NED # (%)	DoD # (%)
Primary	15				
Resected, residual	11	5 (45)	1 (9)	1 (9)	4 (36)
Unresectable for cure					
Resected after XRT	4	3	1	0	0
Recurrent	36				
Resected, residual	21	7 (33)	2 (10)†	4 (19)	8 (38)
Unresectable for cure	15	7 (47)	4 (27)	0	4 (27)†
Resected after XRT	13	7	3	0	3
Never resected	2	0	1	0	1
Total	51	22 (43)	8 (16)	5 (10)	16 (31)

† One patient in each group had solitary liver metastasis resected before IORT.

NED = no evidence of disease progression.

DoD = dead of disease.

XRT = external irradiation.

Kaplan-Meier survival curves are shown in Figures 1 and 2. The 4-year actuarial survival rate (Fig. 1A) is 53% in patients who had primary disease and 23% in those with recurrence. When five patients who died with no evidence of disease were censored at time of death, the survival rates are 57% and 28%, respectively (Fig. 1B). The association of treatment sequence to survival is demonstrated in Figure 2. Since only four patients with primary disease presentation received high-dose preoperative external irradiation, the current separation in survival curves should be interpreted with caution.

Incidence and Patterns of Failure

Incidence and patterns of failure were evaluated in detail. In the total group, 24 of 51 patients (47%) have evidence of disease progression (primary 6 of 15, 40%; recurrent 8 of 36, 50%). Central failure (CF) within the IORT boost field has been documented in only one patient (2% of patients at risk or 4% of failures) and local failure (LF) within the external beam field in eight patients (2 of 15 primary, 13%; 6 of 36 recurrent, 17%). Distant metastasis has occurred in 18 patients (4 of 15 primary, 27%; 14 of 36 recurrent, 39%). Peritoneal seeding has been documented in only four patients (8%) with an equivalent risk in primary and recurrent disease presentation.

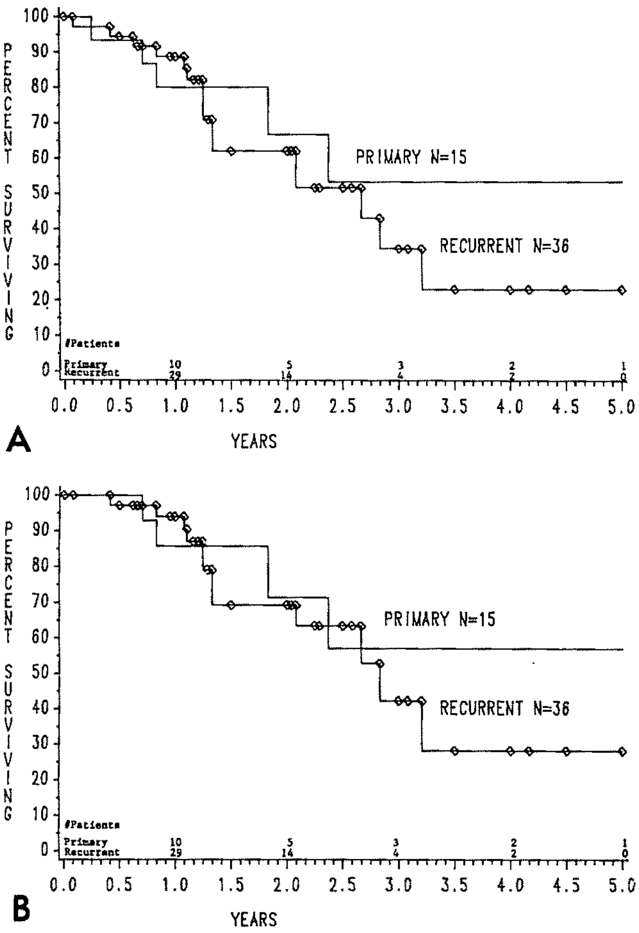

FIG. 1A and B. Kaplan-Meier survival curves for locally advanced colorectal cancer treated with IORT and external beam irradiation with 5FU. *A*. Uncensored. *B*. Censored for death with no disease. # of patients = # alive at interval.

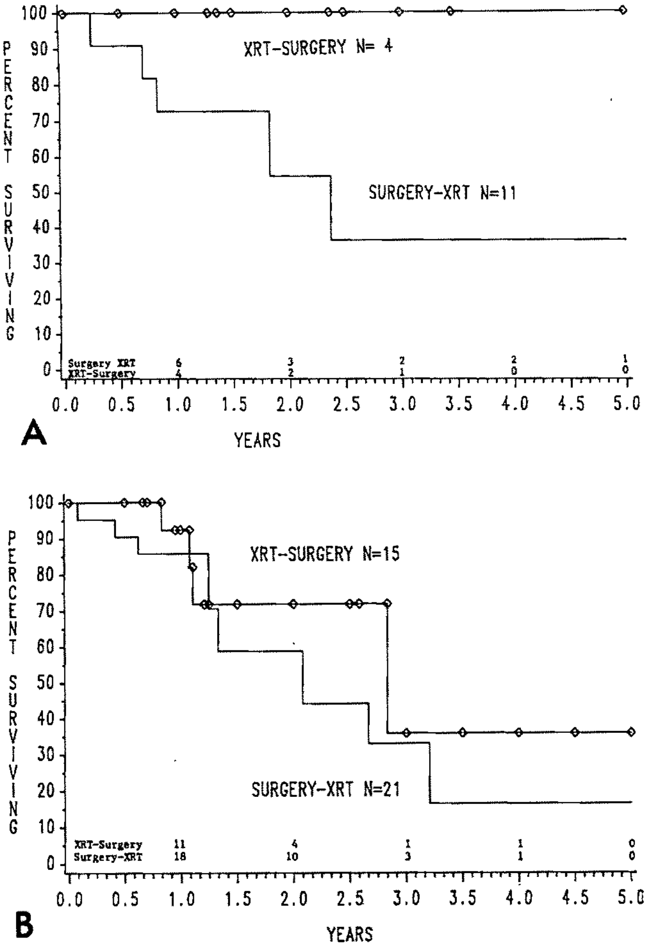

FIG. 2A and B. Kaplan-Meier survival curves with regard to sequence of surgery and irradiation. *A*. Primary disease. *B*. Recurrent.

Patients at risk less than 1 year were excluded from detailed failure analyses in Tables 5–7. The incidence of both total and distant failure remains higher in recurrent *versus* primary disease (Table 5). The impact of resection on local failure (within external irradiation field) and total failure is seen in Table 6. There was a trend for a decrease in the total failure incidence with gross total resection *versus* partial resection *versus* unresected (5 of 13, 38%; 13 of 26, 50%; 2 of 2, 100%). As shown in Table 7, the local failure incidence was lower in patients who received 5FU during external irradiation (1 of 11, 9% *vs.* 6 of 31, 19%).

Complications

An indepth analysis of complications seen in patients with pelvic IORT at our institution is the subject of

TABLE 5. *Incidence and Patterns of Failure: Colorectal IORT*

			Patterns of Failure (Any Component)†							
	Failures		CF		LF		DM		PS	
Disease Category	#	(%)	#	(%)	#	(%)	#	(%)	#	(%)
Primary	5/12	(42)	0		2	(17)	4	(33)	0	
Resected, residual	4/8		0		2		3		0	
Resected after XRT	1/4		0		0		1		0	
Recurrent	18/32*	(56)	1	(3)	6	(19)	14*	(44)	3*	(9)
Resected, residual	10/19		1		2		8		2	
Resected after XRT	6/11		0		3		4		1	
Unresectable	2/2		0		1		2		0	
Total	23/44	(52)	1	(2)	8	(18)	18	(41)	3	(7)

* One patient in each group had solitary liver metastases resected at IORT; therefore, failure in 16 of 30 (53%), DM in 13, PS in 2.

† Seven patients at risk <1 year are excluded from this analysis.

CF = central failure within IORT field.

LF = local failure within external radiation field.

DM = distant metastasis.

PS = peritoneal seeding.

another report (E. Shaw, et al. Am Radium Society Proceedings 1987, unpublished observations). Morbidity related to nerve (Table 8) and ureter were of the most interest and will be summarized here. Symptomatic or objective neuropathy occurred in 12 of 37 (32%) pelvic IORT patients at risk ≥12 months. This was manifested as pain in all 12 patients (resolved in 5 and severe in 3), sensory in eight patients (none were severe), and motor in seven patients (resolved in 1 and only 1 severe). The IORT boost field encompassed 12 ureters in the 37 patients. Nine ureters were unobstructed before IORT, and subsequent hydronephrosis developed in four (44%). Three ureters were initially obstructed by tumor, and hydronephrosis resolved in two.

Discussion

In the United States IORT trials, some of the most favorable results have been obtained in patients who have colorectal lesions that are unresectable for cure, have residual disease after resection, or have recurrent but localized disease. Although this site did not receive much emphasis in Japanese trials,[11,12] in a recent combined analysis, five of 14 patients with IORT for colon cancer were alive.[12] One patient was alive and free of disease 9 years and 8 months after treatment and one patient at 10 years despite retroperitoneal invasion and unresected nodal disease in both.[11] The two largest reported colorectal IORT analyses are the current series and previous data from Massachusetts General Hospital.[6,7,13] Potential improvements in local control and survival with aggressive combined treatment approaches, including IORT, are most evident when compared with results achieved with previous or current "standard approaches," *i.e.*, primary irradiation combined with chemotherapy or immunotherapy or external beam irradiation combined with total or subtotal resection.

TABLE 6. *Impact of Resection on Local and Total Failure: Colorectal IORT**

	Primary				Recurrent			
	LF		Total		LF		Total	
Amount of Residual	#	(%)	#	(%)	#	(%)	#	(%)
Miscroscopic (gross total removal)	0/6		2/6		2/7	(29)	3/7	(43)
Gross	2/6		3/6		2/20	(10)	10/20	(50)
Unresected	—		—		1/2		2/2	
Total	2/12	(17)	5/12	(42)	5/29	(17)	15/29	(52)

* 10 patients excluded from analysis. Seven at risk <1 year; two with solitary liver metastases resected prior to IORT (subsequent DM, PS); one who received only 2520 rad/14 fractions external because of previous 4000 rad (subsequent LF & DM).

LF = local failure in external beam field.

DM = Distant metastasis.

PS = Peritoneal seeding.

Total = total failures, any pattern.

Primary Irradiation

With locally advanced primary or recurrent colorectal lesions, external radiation has been shown to have good palliative and occasional curative value. With primary lesions, Wang and Schulz[14] reported long-term survival in 12.5% (2 of 16) patients who were inoperable (medical or surgical). Good or excellent palliation is obtained in approximately 75% of patients with recurrence, but the long-term survival rate is $\leq 5\%$.[2,3,14–16]

Cummings et al. presented a series from the Princess Margaret Hospital[1] in which 67 patients with tumor fixation of a primary lesion were treated with radical external beam irradiation without resection. Local control was achieved in only six of 67 patients (9%), and the 5-year actuarial survival rate was 2%.

In a recent Mayo Clinic analysis, 44 patients with locally advanced rectal cancer (unresectable in 7, resected but residual in 7, locally recurrent in 30) received 5000-rad split-course pelvic irradiation with or without adjuvant immunotherapy.[2] In the 31 patients in whom site of initial tumor progression could be evaluated, 28 (90%) had local progression within the radiation field, and in 17 patients (55%), it was their only site of disease.

Resection and External Irradiation

In separate analyses from the Massachusetts General Hospital (MGH)[17] and Albert Einstein (AE),[18,19] the incidence of local failure (LF) after subtotal resection and external beam irradiation for primary lesions varied by the amount of residual disease. With microscopic residual, the incidence was 15–26% (AE, 2 of 13; MGH, 8 of 31) but with gross residual it was 50–54% (AE, 9 of 18; MGH, 13 of 24).

With primary lesions that are unresectable for cure due to tumor fixation to an unresectable structure, preoperative radiotherapy has been used in an attempt to reduce lesion size and tumor viability, allow resection, and possibly improve local control and survival.[20–22] Although resection can be achieved in 50–75% of such patients after 4500–5000 cGy given over 5–6 weeks, the incidence of local recurrence in resected patients ranged from 35–45% in series from Tufts,[21] MGH,[22] and Oregon.[20]

External Irradiation, IORT, Resection and 5FU

A combination of external irradiation and IORT allows the safe delivery of higher effective doses of irradiation than can be delivered with only external beam techniques. With external irradiation, adjacent dose-limiting organs, such as the small bowel, limits doses to 4500–5000 cGy given in 25 to 28 fractions in many patients.[8,9,15,16] Even when the small bowel can be excluded, doses within boost fields are usually not carried beyond 6000–7000 cGy. The biologic effectiveness of single-dose irradiation is considered equivalent to 2–3 times that quantity of fractionated external beam treatment.[23] In view of that, the effective dose in the intraoperative boost field when added to the 4500–5000 cGy delivered in 25 to 28 fractions with external beam techniques is 6500–8000 cGy for an IORT dose of 1000 cGy, 7500–9500 cGy with a 1500-cGy boost, and 8500–11000 cGy with a 2000-cGy IORT dose.

TABLE 7. *Incidence of Local Failure: XRT with or without 5FU**

Disease Category/ XRT Sequence	XRT + 5FU #	XRT + 5FU (%)	XRT only #	XRT only (%)
Primary				
Postop XRT (2/8)	0/3		2/5	(40)
Preop (0/4)	0/1		0/3	
Recurrent				
Postop XRT (3/20)	0/5		3/15	(20)
Preop XRT (2/10)	1/2		1/8	(13)
Total	1/11	(9)	6/31*	(19)

* Eight patients excluded from this analysis. Seven at risk <1 year and one received only 2520/14Fx (previous 4000 rad).

Survival and disease status. In the initial MGH report of 32 patients treated with IORT combined with external irradiation,[6] survival was higher than that seen in previous MGH series of patients treated with external beam techniques with or without resection.[3,17,22] In patients with residual disease after subtotal resection of the primary lesion, although five of seven patients with IORT had gross residual, survival rates paralleled the external beam curve of patients with microscopic residual disease.[6] For patients who initially had unresectable primaries in whom external irradiation preceded resection, survival at 1 and 2 years was statistically better in 16 patients who received an IORT supplemental dose when compared with historic controls treated only with external irradiation and resection. These advantages did not appear to be due to a difference in patient selection. In an updated analysis by Tepper et al.,[13] the 4-year actuarial survival rate is 50% in IORT patients who have

TABLE 8. *Characteristics of Neuropathy: Pelvic Colorectal IORT**

Characteristic	Incidence	Severe†	Resolved
Pain	12/37 (32%)	3/12 (25%)	5/11 (45%)‡
Sensory	8/37 (22%)	0/8	—
Motor	7/37 (19%)	1/7 (14%)	1/7 (14%)

* Patients with follow-up <1 year or extrapelvic IORT are excluded.
† Definition by characteristic: pain, intractable; sensory, disabling sensory loss or intolerable paresthesia; motor, severe weakness.
‡ One patient lost to follow-up.

primary disease and 25% in those with recurrence (the expected long-term survival rate for locally recurrent lesions is 5% when treated with standard techniques).[14-16] The poorer survival rate in the recurrent *versus* primary disease presentation is due to a higher incidence of both local and systemic failure in the recurrent group.

In the current IORT series of 51 patients, survival results parallel those achieved at MGH (Fig. 1). Thirty of 51 patients (59%) are alive, and 22 (43%) are free of disease. The actuarial survival rate at 4 years is 53% and 23% with primary *versus* recurrent disease presentation (survival rate is 57% and 28% if deaths from unrelated causes are censored). Disease progression has been documented in 56% of patients with recurrence at risk ≥1 year *versus* 42% with primary disease. In both series, overall and disease-free survival are somewhat better when irradiation precedes resection, but this may be a function of case selection.

Distant metastases (DM). In the IORT series from both institutions, systemic failure has been more common in patients when surgery preceded high-dose irradiation and with recurrent *versus* primary disease presentation. In the initial MGH series,[6] in patients with primary disease, the comparative systemic failure incidence was three of six patients (50%) when surgery preceded irradiation *versus* two of 16 patients (13%) when the sequence was reversed. That trend is also seen in the current series in patients at risk ≥1 year (DM in 11 of 27 or 41% when surgery preceded irradiation *vs.* 5 of 15 or 33%). Whether the lower incidence is due to a different treatment sequence (*i.e.,* preoperative irradiation may alter implantability of cells spread at time of resection) or is due to case selection cannot be ascertained, as choice in treatment sequence was not controlled in either series. The incidence of DM in the current series is 44% *versus* 33% for recurrent *versus* primary lesions.

Local control. Most local regrowths in the MGH IORT series[6,13] and all in the current series have been in patients who had recurrent lesions or gross residual after partial resection of primary lesions. In the initial MGH report, local control appeared to be improved in both the patients with residual disease and initially unresectable disease who received an IORT boost[6] *versus* those who received only external beam irradiation.[17,22] In their updated analysis,[13] local control at 4 years is 85% *versus* 30% for primary *versus* recurrent disease with a definite advantage in patients with gross total resection (≤ microscopic residual) *versus* partial resection or unresected disease. In the current series, the addition of 5FU during external irradiation resulted in a possible decrease in the risk of local recurrence (1 of 11 patients or 9% with 5FU, 6 of 31 patients or 19% with radiation alone). An improvement in local control with radiation plus chemotherapy *versus* radiation alone has also been seen in two randomized adjuvant rectal trials.[24-26]

Morbidity. In patients with locally advanced colorectal malignancies, it is difficult to place the question of morbidity after treatment into clear perspective. If external radiation is used as the main treatment modality, ≥90% of patients had local persistence or recurrence of disease in analyses from the Princess Margaret Hospital and the Mayo Clinic and most were dead at 3–5 years (end result is nearly 100% morbidity). If aggressive surgery with pelvic exenteration or distal sacrectomy is performed alone or in conjunction with external irradiation, significant morbidity ensues even if the tumor is controlled.[16]

With combinations of external irradiation, surgery, and IORT (with or without 5FU), subsequent problems with healing or infection could be related to the advanced stage of tumor growth or regrowth (10 of the initial 32 MGH patients and 36 of the 51 Mayo patients had recurrence), the difficulty of the surgical resection or reresection, and aggressive radiation. A significant increase in soft tissue complications has not been encountered in the MGH series of patients who received an IORT boost in comparison to patients with similar disease extent treated with external beam irradiation alone.[27] Some problems with delayed wound healing have been encountered in IORT patients in whom an infection in the pelvis or a perineal wound developed after preoperative irradiation and abdominoperineal resection.[4,6,7] Neither the magnitude nor the incidence of such problems was increased when compared with patients treated with only preoperative irradiation and resection at MGH[22,27] or at other institutions.

Problems with delayed pelvic pain or paresthesias have been reported in series from both institutions, and motor difficulties have also been discussed in the current analysis. It is uncertain whether these findings are a result of irradiation fibrosis with nerve entrapment, direct neuropathy, or a combination of both. The incidence in the current series is higher than from MGH and is probably a function of a larger percentage of patients presenting with recurrent disease (with pre-existent pain and nerve damage) and the use of higher IORT doses (in the initial 32 MGH patients, the highest IORT dose was 1500 cGy and in the current series the IORT dose exceeded 1500 cGy in 28 of 51 patients). Motor deficits have been rare in contrast to a recent report from NCI.[28] None were reported in the MGH analyses and there was only one case of severe magnitude in the current series.

The finding of ureteral narrowing with IORT plus external irradiation is not surprising in view of animal studies from NCI[29,30] and Colorado State University.[31] In the current series, four of nine (44%) previously unobstructed ureters became partially or totally obstructed when included in the IORT field, and hydronephrosis resolved in two of three that were obstructed by tumor. If tumor is adjacent or adherant to the ureter and is uncontrolled, ureteral obstruction occurs in nearly 100% of patients. Our policy, therefore, is to include the ureter within the IORT field in the presence of tumor adherence or involvement.

Conclusions and Future Possibilities

The long-term results of an aggressive treatment approach for locally advanced malignancies are dependent on disease presentation (primary *vs.* recurrent), on the metastatic potential of the lesion, and possibly on the sequencing of external irradiation and resection. Distant failures in the MGH and Mayo IORT colorectal series were most common in patients with recurrent disease or who had partial resection of primary disease before moderate dose external irradiation. With both primary and recurrent disease, it may be preferable to deliver the external irradiation before attempted resection and IORT boost (deliver 4500–5000 cGy in 25 to 28 fractions; restage approximately 4 weeks later, do partial or gross total removal, and give IORT boost if feasible). Theoretical advantages of this sequence include: (1) potential alteration of implantability of cells, which may be disseminated at the time of partial surgical resection (spread of cells is more likely in patients with gross transection of tumor); (2) deletion of patients with metastases detected at the restaging workup or at laparotomy, thus sparing the potential risks of an IORT boost; and (3) reduction of the treatment interval between external and intraoperative radiation. If the resection and IORT boost are the initial phase of treatment and the patient has postoperative complications, the interval to the start of external irradiation may be prolonged to the degree that the combined IORT plus external doses do not have an additive antitumor effect but only an additive effect on normal structures (*i.e.*, added risk but no potential gain).

Since similar encouraging trends exist in separate colorectal IORT analyses from MGH and Mayo, expansion or refinement of IORT approaches seem warranted. Such combined treatment programs appear to improve local control and possibly survival of locally advanced colorectal lesions. In an attempt to further decrease the incidence of local failure, the role of radiation dose modifiers during external irradiation (5FU) or IORT (sensitizers, hyperthermia, etc.) needs to be evaluated. Treatment of the liver and/or peritoneal cavity with intraperitoneal chemotherapy or radiocolloids, infusion chemotherapy, external radiation, or combinations may be necessary in patients who have high metastatic potential. If either infusion chemotherapy of the liver[32,33] or intraperitoneal chemotherapy decreases the incidence of liver metastases in ongoing trials with colon cancer, it would be worthwhile to consider the same approach with locally advanced colorectal cancer. Even with locally recurrent lesions, the aggressive multimodality approaches have resulted in projected long-term survival rates of 25–30% *versus* an expected 5% with conventional techniques. Randomized trials will be needed that compare standard treatment to treatment that includes an IORT boost to see if previous observed differences are true advantages or are merely due to a difference in case selection.

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Functional and Oncologic Results after Coloanal Anastomosis for Low Rectal Carcinoma

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Thirty-five patients who had adenocarcinoma of the middle third of the rectum were treated by resection and coloanal anastomosis. The aim of this study was to assess functional and oncologic results of an original technique of coloanal anastomosis. There was no operative mortality, and operative morbidity consisted of seven anastomotic leaks with two failures. Among 31 patients assessed for functional results only one had unsatisfactory results. Good continence was obtained within a few weeks for the 30 patients who had satisfactory results. No patients were lost to follow-up, which was over 5 years in 24 patients (68%). The 5-year survival rate was 64%, identical to that for other series.

INDICATIONS OF SPHINCTER-SAVING procedures have become more frequent for carcinomas of the middle third of the rectum since a 2-cm margin is considered sufficient for distal clearance.[1,12,29,47] Whereas the results of Babcock's operation and low anterior resections have been extensively studied, there are only a few reports about resection with coloanal anastomosis (CAA). We report a series of 35 manual CAA on the dentate line after macroscopically curative resection of invasive adenocarcinomas of the low rectum. The aims of this study are to assess the reliability of an original technique of CAA and its functional and oncologic results.

Patients and Methods

Patients

From March 1969 to June 1984, 35 patients had rectal excision with peranal CAA in our surgical unit. There were 22 men and 13 women aged 31–83 years (mean: 55 years). They all had a rectal adenocarcinoma, which had infiltrated at least the submucosa and was mobile at digital palpation. According to Dukes' classification,[7] 12 cases were graded A, 11 were graded B, and 12 were graded C1. Tumor growth was circular in 4 cases, occupied more than a quarter of the colonic circumference in 22 cases and less in nine. Distances between the distal growth margin and the anal verge are indicated in table 1. This distance was 9 cm or less in 25 cases, and between 9 and 12 in the remaining ten.

Surgical Technique

The patient was placed in the lithotomy position. A long midline laparotomy was made. The abdominal procedure used was identical to the one for abdominoperineal excision: it comprised high ligation of the inferior mesenteric artery, division of the lateral ligaments on the pelvic wall, and complete mobilization of the rectum down to the level of the levators and of the anorectal junction. The sigmoid colon was divided and closed. The perineal procedure consisted of exposing the dentate line by rectal eversion followed by CAA. It started with a gentle anal stretch and irrigation of the rectal stump with an antiseptic solution after a rectal clamp had been positioned. In cases of low and/or small tumor growth, the stump was everted with the tumor after division and closure. In cases of bulky and/or higher growth, the rectum was divided and closed below the tumor, and the lower stump everted. In all cases the distal division was made on the dentate line, which was progressively exposed by a series of stay sutures. The specimen removed was then opened to ensure that a minimum distal margin clearance of 2 cm had been preserved, in which case CAA was performed. The left colon was completely mobilized by dividing the inferior mesenteric vein at the lower margin of the pancreas; this maneuver enables the distal end of the colon to be easily

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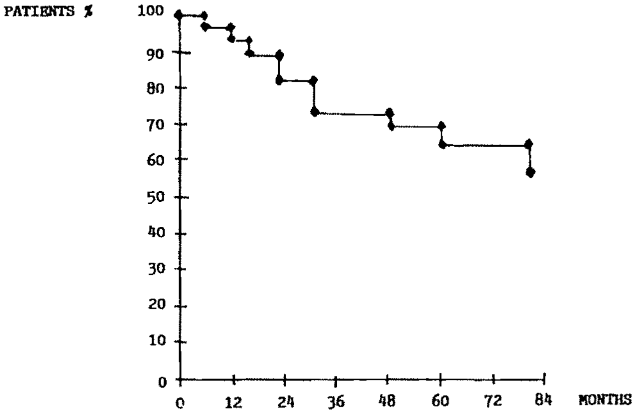

FIG. 1. Actuarial survival curve according to Kaplan-Meier.

drawn toward the anus. Anastomosis was performed manually, quadrant by quadrant, using a one-layer series of total interrupted sutures of slowly absorbable material. No anal retractor was used. The anastomosis was located on the dentate line, and after completion returned spontaneously into the pelvis, at the top of the external sphincter. A defunctioning colostomy was systematically performed, usually exteriorized in the left lower quadrant. The absence of anastomotic leak was systematically checked by contrast enema, 2 months after excision, before colostomy closure. No adjuvant therapy was used.

Assessment

All patients were assessed for continence and defecation and for local and distant oncologic recurrences. The acturial curve of survival was constructed by the method of Kaplan-Meier.[19]

Results

Mortality and Morbidity

There were no postoperative deaths, either after resection or colostomy closure. Outcome was simple and continuity restored after 2 months in 26 patients (74%). Specific morbidity consisted of anastomotic leak, which occurred in seven of the remaining nine patients (20%). Four of these leaks (11%) were symptomatic with anal suppuration but no reoperation was necessary. The three others (9%) were discovered on the routine contrast enema. In six of these seven patients, colostomy was subsequently closed with two failures (recurrent anal suppuration necessitated a second colostomy in 1 patient and the other had a persistant vaginal leak). In three of the nine patients with a complicating outcome, continuity was never restored because of an early pelvic tumor recurrence. There were no cases of colonic necroses or anastomotic stricture even in patients who had a leak.

TABLE 1. *Distal Margin According to Duke's Classification*

Dukes' Stage	Less than 6 cm	6–9 cm	9–12 cm	Total
A	5	5	2	12
B	0	9	2	11
C	0	6	6	12
Total	5	20	10	35

Functional Results

Functional results were assessed in 31 patients. They were considered unsatisfactory in one patient. In 30 patients, flatus and stool could be differentiated and retained and the need to defecate was felt. None of these patients wore pads, but minimal leaks occurred in some patients in cases of diarrhea. In the first months after colostomy closure, 50% of the patients had frequent bowel actions; 1 year later, stool frequency was 2/24 h in 27 patients and 3–6/24 h in three patients. In these 30 patients, no intubation, dilatation, diet, or medication were necessary. The one unsatisfactory result was due to a persistant vaginal leak.

Oncologic Results

No patients was lost to follow-up, which was over 5 years in 24 patients (68%). The actuarial curve of survival is shown in Figure 1. Six patients (17%) had a pelvic tumor recurrence and another patient (5%) had a recurrence on the anal canal below the anastomosis. According to Dukes' classification, initial tumor growth was classified as B in one of the seven patients and C1 in the other six patients. There was no local recurrence in the cases classified as A. The distal clearance margin was over 2 cm in all patients. It was less than 3 cm in one patient, between 3 and 5 cm in five patients, and between 5 and 7 cm in one patient. In no case did the pathologic examination of resected specimens reveal involvement of the distal margin. Five of the seven local recurrences occurred within 3 years of resection. Of the remaining two recurrences, one, which was paravaginal, occurred 6 years after resection and was treated by local excision and radiotherapy; 4 years later (June 1986) the patient is alive and free of disease. The last patient whom recurrence was infra-anastomotic was treated by curietherapy and radiotherapy; at first he refused abdominoperineal excision, but this was performed 1 year later.

Discussion

There were no postoperative deaths in our series, and the mortality rate reported after CAA in other series was always below 4%.[6,24,30] This rate is comparable with the rates for abdominoperineal excision and low anterior resection. The main postoperative complication was anastomotic leak.[11] It occurred in 20% of our patients, but was only clinically significant in 11%. In the other series of CAA, the rate of anastomotic leak ranged from 9.7 to

11.9%, but no routine radiologic examination of the anastomosis was made and only symptomatic leaks were taken into account. The rate of anastomotic leak after anterior resection was usually about 9% except for Localio et al., who reported a rate of 1%.[24,25,43,44,48,50] The risk of leak does not seem to be reduced when stapled anastomoses are performed.[10] The frequency of leak after CAA is not much higher than after low anterior resection, but we believe it justifies the systematic use of a covering colostomy, which reduces the risk of leak.[6] The covering stoma is not always used by Localio et al., who defined a high-risk group, but they reported four cases of generalized peritonitis, one of them fatal. Thus, in the current series, no leak led to peritonitis or death, and only two of the seven leaks led to permanent functional failure (5.7%).

It is not evident that a transphincteric approach facilitates resection or suture, and we believe that section of the anal sphincter is open to criticism, even when it is carefully repaired.[21,51] We believe that the advantages of our technique are good exposure of the dentate line, which facilitates suture, no stretching of the anal sphincter with a permanent retractor, and the absence of septic contamination of the pelvis.[37] The functional results of the different methods of CAA are comparable.[6,23,24,30,31,37] Satisfactory continence is usually obtained within a few weeks of colostomy closure. No case of night leak has been reported. Only one author reported the need for protection pads in 50% of his patients and flatus incontinence.[16] On the other hand, defecation disorders were reported in most series.[6,23,30,31] Patients pass several stools a day, sometimes with urgency, with variable frequency from one day to another. Occasional minor leaks are possible, especially in the case of diarrhea. In our series, as in others, functional results usually improved 1 year after surgery. This might be connected with the possible reappearance of the rectoanal inhibitory reflex, as showed by manometric studies.[42] The same type of defecation disorders are reported after very low anterior resections, especially when less than 4 cm of rectum are preserved.[2] They are due to the disappearance of the rectal reservoir. The construction of a colonic pouch combined with CAA might be useful in the early postoperative months.[22,33,46] There were no anastomotic stenoses in the current series or in most of the others. Only Keighley and Matheson reported cases of such stenosis, but with they used a rectal muscular cuff and some of these stenoses were due to pelvic tumor recurrence.[14] The general absence of stenosis is probably due to the performing of true sutured anastomosis, contrarily to Babcock's procedure, which is associated with a high rate of stenosis.[15,17,41] This is one of the major advantages of CAA *versus* Babcock's operation. The satisfactory clinical results for CAA confirm that the preservation of the levators ani and of the anal canal leads to good continence despite the absence of rectal ampulla.[3,18] In fact, the puborectalis has sensory receptors when it is stretched in addition to its motor role.[34,35] Therefore, the nerves, located on the endopelvic side of levators ani, should be preserved.[38] Furthermore, the colonic stump should be sufficiently mobile to fill the sacral concavity, thus constructing an anal angle and making contact with the levators. The occurrence of pelvic sepsis may lead to fibrosis and alter the continence.[20]

The 5-year survival rate of 64% in this series is identical to that for other series. The rates reported for anastomotic recurrence are very low (1.3–2.3%). Here, we only observed one recurrence below the anastomosis without pelvic recurrence, but no anastomotic recurrence. Our pelvic recurrence rate of 17% is comparable with that of Localio (14.6%) and Nicholls (13%). Like us, these authors did not use any complementary therapy. In several series, the results of abdominoperineal excision have been compared with those of sphincter-saving procedures in treating carcinomas of the middle third of the rectum.[25,30,43,44,48,49,50] In cases of curative resection, 5-year survival rates range from 55 to 65%, whether total excision or restorative procedure is performed. All these studies are retrospective, and their Dukes' stage distribution are not equivalent; therefore, the distribution for abdominoperineal excision is unduly pessimistic. However, prognosis seems more closely related to the tumor stage than to the type of surgical procedure.[24,30,48] In two series matched for Dukes' staging, Williams showed that there was no difference in survival or recurrence, whether middle-third lesions were treated by an abdominoperineal excision or a sphincter-saving procedure. Similar results are reported by Wilson, Localio, and McDermott.[23,25,49] In our series, there were no local or distant recurrences in the 12 patients with a Dukes' A tumor. Of the 11 patients with a Dukes B tumor, three died of cancer (2 metastases and 1 local recurrence). Three of the five deaths that occurred among the 12 patients with Dukes C1 growth were due to an isolated pelvic recurrence.

The location of the lesions treated by resection and CAA did not influence the rate of pelvic recurrence. It seems that this rate only rises when a lesion is located less than 5 cm from the anal verge.[5] Pathologic clinical studies show that the distal clearance margin can be reduced to 2 cm.[12,18,39,40,47] However, this margin should not be systematically reduced to 2 cm, as some authors believe this is insufficient in cases of poorly differentiated or Dukes' B tumors.[4,28] We believe that in lesions encroaching on the lower third of the rectum this margin is only acceptable when they are small and mobile. Intrarectal ultrasound might help preoperative staging of wall extension.[13] In cases of bulky and higher growths, CAA allows a wider margin of clearance than low anterior anastomosis. In resection of middle-third and some lower-third rectal carcinomas, sphincter and pelvic floor saving seems possible without increasing the risk of local recurrence. Finally, it is difficult to compare the results of CAA with those of other sphincter-saving procedures (transanal excision, electrocoagulation, and irradiation) for which pathologic staging is not available.[7,32,45]

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Colorectal Villous and Tubulovillous Adenomas Equal to or Greater than Four Centimeters

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The records of 237 patients treated for benign and malignant villous and tubulovillous adenomas at Roswell Park Memorial Institute from 1963 to 1987 were reviewed. Sixty-five adenomas were ≥4 cm and form the basis of this report. Fifteen (23%) were in the cecum, 3 (5%) in the right colon, 1 (1%) in the splenic flexure, 10 (15%) in the sigmoid colon, and 36 (55%) in the rectum. The most common symptoms were rectal bleeding (70%), mucus diarrhea (44%), constipation (22%), and tenesmus (19%). Fifty-five (85%) of these large adenomas contained invasive adenocarcinoma and one in situ carcinoma. Two thirds of invasive carcinomas arose from predominantly villous adenomas and one third from tubulovillous adenomas. Half of all malignant adenomas demonstrated metastases to regional lymph nodes or distant metastases. Seven malignant adenomas (12%) were associated with synchronous adenocarcinomas of the colon, and 29% of malignant adenomas were associated with synchronous adenomatous polyps, principally tubular type. Four of nine benign, large adenomas were associated with synchronous adenomas but with no adenocarcinomas. No relationship was found between the size of the adenoma, location, or Dukes' stage. Though the incidence of in situ and invasive carcinomas is clearly related to the size of the adenoma, a linear relationship could not be demonstrated.

ADENOMAS of the colon and rectum represent true neoplastic growths and are generally regarded as potentially premalignant lesions. Villous and tubulovillous adenomas together constitute from 19–53% of colorectal adenomas.[1–3] The villous component has been implicated as the determinant more likely to be associated with in situ and invasive adenocarcinoma.[2–9] The other determinant has been directly related to size, with a proportionate increase in invasive carcinoma in larger lesions.[2,3,9–11] However, adenomas with a villous component are recognized for their ability to attain large dimensions without incurring concomitant malignancy, and invasive carcinoma is not uncommonly found in villous or tubulovillous adenomas <2 cm in size.[2,3,7,9–11] Given the uncertainty of malignant involvement in an adenoma, particularly of the larger lesions, various clinical and histologic criteria have been reported concerning polypectomy *versus* surgical resection.[7,12–16] Earlier reviews have advocated a conservative approach toward management of villous adenomas, even in the presence of invasive carcinoma, based on the contention that these lesions demonstrated a benign course with little predilection for metastases.[10,11,17]

Studies to date on colorectal adenomas have not discriminantly looked at large adenomas with a villous component; conversely, since the inception of the colonoscopy era, the literature has focused primarily on adenomas that can be removed by virtue of colonoscopy alone, often with the exclusion of malignant lesions.

The purpose of this review is to examine the clinical nature of villous and tubulovillous adenomas ≥4 cm in diameter and to correlate this with location of the lesions, incidences of in situ and invasive adenocarcinoma, and Dukes' staging.

Materials and Methods

This retrospective study reviews the medical records of 237 patients with villous or tubulovillous adenomas of the colon and rectum treated at Roswell Park Memorial Institute from 1963 to 1987. Only those patients with histologically confirmed benign and malignant villous and tubulovillous adenomas were included. Pa-

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TABLE 1. *Site* Versus *Dukes' Stage of Malignant Villous Adenomas*

		Dukes' Stage							
Site	Unknown	A	B_1	B_2	B_3	C_1	C_2	C_3	D
Cecum	0	0	2	2	0	4	1	0	4
Right colon	0	0	1	0	0	1	0	0	0
Sigmoid	0	1	3	2	0	1	0	0	1
Rectum	0	0	7	6	1	8	0	2	5
Total (N = 56)	4	1	13	10	1	14	1	2	10

tients with papillary adenocarcinoma, polypoid adenocarcinoma, and equivocal histologic diagnoses were excluded. By these criteria, six patients were excluded from the study, and of the remaining 231 patients, 63 patients (27%) had villous or tubulovillous adenomas ≥4 cm. Two patients each had two synchronous villous lesions greater than 4 cm in diameter, constituting a total of 65 villous tumors. There were 28 women and 35 men with a median age of 66 years (range: 45–82 years).

Dimensions of the villous tumors were measured along their greatest diameter. Direct measurements of the surgical specimen were available in all instances, and if this was at variance with measurements obtained on colonoscopy, the more conservative measurement was used. All tumors resected at Roswell Park Memorial Institute were subjected to lymph node clearance using alcohol extraction of fat and fixation of lymph nodes in cedar oil.[18] Pathologic staging was performed according to the Gastrointestinal Tumor Study Group (GITSG) as follows: Dukes' A: mucosal invasion; Dukes' B_1: tumor through mucosa but no serosal penetration; Dukes B_2: serosal penetration; Dukes' B_3: serosal penetration with direct involvement of adjacent organs; Dukes' C_1: 1–4 lymph nodes positive for tumor; Dukes' C_2: more than 4 positive lymph nodes; Dukes' C_3: involvement of adjacent organ and positive lymph nodes; and Dukes' D: distant metastases. Patients were analyzed according to the site of primary villous tumor, frequency of benign *versus* malignant adenoma, pathologic stage in regards to site of the primary lesion and size, and site of the tumor in relation to size.

Results

Of 65 total villous tumors, 55 (85%) were found to contain invasive adenocarcinoma, defined as invasion through the muscularis mucosa, and one tumor (1%) contained *in situ* adenocarcinoma. The remaining nine (14%) villous tumors contained no foci of carcinoma. Twenty-one villous tumors were diagnosed prior to 1973 by barium enema and proctosigmoidoscopy, of which only two adenomas were found to be benign. Forty-four additional villous tumors were diagnosed after 1973, principally by colonoscopy, and 37 of these contained adenocarcinoma. The location of the primary villous tumors was as follows: cecum, 15 (23%): 13 contained carcinoma and two were benign; ascending colon, three (5%): two contained carcinoma and one was benign; splenic flexure, one was benign; sigmoid, 10 (15%): eight contained carcinoma and two were benign; rectum, 36 (55%): 33 contained carcinoma and three were benign.

Though the number of villous tumors of the rectum diagnosed prior to and after the institution of colonoscopy were similar (16 and 20, respectively), three malignant villous adenomas of the right colon and one of the sigmoid were diagnosed prior to 1973, while 12 malignant villous adenomas of the right colon and seven of the sigmoid were diagnosed subsequent to the introduction of colonoscopy.

Fifty-six villous or tubulovillous adenomas contained carcinoma. In each case, clear demarcation or transition from benign villous or tubulovillous component to *in situ* or invasive carcinoma was apparent on histologic examination. Since all carcinomas arose either centrally or along one border of the adenoma, measurements were based on the extent of the grossly benign component. The adenocarcinomas were as follows: one Dukes' A, 13 Dukes' B_1, ten Dukes' B_2, one Dukes' B_3, 14 Dukes' C_1, one Dukes' C_2, 2 Dukes' C_3, and ten Dukes' D carcinomas (Table 1). In four additional rectal villous adenomas with invasive carcinoma, Dukes' staging was not possible because three patients refused abdominoperineal resection following transanal or transsacral resection of the villous adenoma, and one patient underwent transanal resection of a malignant villous adenoma in conjunction with right hemicolectomy for a synchronous cecal adenocarcinoma. Of 15 malignant villous adenomas of the cecum and right colon, 66% were metastatic to lymph nodes, and of 29 staged malignant villous adenomas of the rectum, 50% were metastatic to lymph nodes (Table 1).

Differentiation of the 55 villous adenomas with invasive carcinoma was as follows: well differentiated, 27; moderately well differentiated, 26; poorly differentiated, 2; and one *in situ* adenocarcinoma. The degree of differentiation of the tumor bore no relation to the site or size of the primary.

Clinically, the most frequent symptoms were rectal bleeding (44 patients) and a change in bowel habits (38 patients), with mucus diarrhea being twice as frequent as constipation. Eight patients experienced tenesmus, six patients experienced vague, crampy abdominal pain, six noted weight loss, one noted a decrease in stool caliber, and one had prolapse of a rectal tumor. Two patients presented with anemia and six patients were asymptomatic with a lesion found either on routine examination of the lower gastrointestinal tract or by fecal occult blood. No patients experienced the syndrome of voluminous diarrhea and hypokalemia. The range of duration of symptoms was from 1 month to 8 years, with a median of 7 months.

Fifty-nine patients underwent 64 procedures for excision or resection of their villous tumor (Table 2). Two patients with metastatic disease underwent colonoscopy only and biopsies of the tumor, and one large villous adenoma was found incidentally at autopsy. Seven patients (12%) had synchronous invasive adenocarcinomas of the colon that did not arise in association with an adenoma. A total of 40 synchronous adenomas of the colon and rectum were found in 16 of the 56 patients (29%) with malignant villous adenomas. The majority of these adenomas were tubular, and of these, one patient had six tubular adenomas of varying size concomitantly with two synchronous malignant, large villous adenomas. Two patients had tubulovillous adenomas containing invasive carcinomas. The remaining polyps were an even distribution of tubular, villous, and mixed tubulovillous adenomas, with the majority containing *in situ* carcinomas. Three of 9 (33%) benign, large villous adenomas were associated with a total of 22 synchronous benign adenomas. One patient harbored 16 tubular adenomas in association with a benign cecal villous adenoma.

In contrast to the adenomas synchronous with malignant, large villous adenomas, the adenomas synchronous with benign, large villous adenomas were in no instance found to contain either *in situ* or invasive adenocarcinomas. Furthermore, in both benign and malignant villous adenomas, the associated adenomas were principally located in the same segment of colon or rectum with the primary villous adenoma.

TABLE 2. *Surgical Procedures for Villous and Tubulovillous Adenomas**

Procedure	Number of Villous Adenomas Without Carcinoma	Number of Villous Adenomas With Carcinoma	Total
Exploratory laparotomy	0	1	1
Total proctocolectomy	0	2	2
Right colectomy	3	11	14
Left colectomy	1	1	2
Sigmoidectomy	0	5	5
Low anterior resection	1	2	3
Abdominoperineal resection	1	17	18
Kraske procedure	1	2	3
Transanal resection	1	6	7
Fulguration†	0	2	2
Polypectomy	1	3	4

* Two patients with metastatic carcinoma (rectal and cecal adenoma) underwent colonoscopy and biopsies of the primary lesion only; one patient had the adenoma found incidentally at the time of autopsy.

† One patient subsequently underwent abdominoperineal resection, and the other patient underwent subsequent low anterior resection.

In regards to metachronous adenocarcinoma of the colon, two patients with malignant villous adenomas of the rectum subsequently developed adenocarcinomas of the right colon within several years, and one patient with a malignant cecal villous adenoma developed adenocarcinoma of the transverse colon 18 months following resection of the first primary. Three patients with malignant villous adenomas of the cecum had previously undergone resection of sigmoid adenocarcinomas. Follow-up concerning metachronous adenomas, however, has not been sufficient to allow for significant data.

The size of the villous and tubulovillous adenomas ranged from 4–20 cm. Four malignant villous adenomas (two cecal and two rectal) were annular but exceeded 4 cm in diameter longitudinally. For benign and malignant villous and tubulovillous adenomas, the mean diameters were 5 cm. The site of the adenoma had no correlation with its size (Tables 3 and 4). When the

TABLE 3. *Size (cm) of Villous Adenomas Without Carcinoma Related to Bowel Site*

Site	Mean	4–4.9	5–5.9	6–6.9	7–7.9	8–8.9	9–9.9	10–10.9	>11
Cecum	4.0	1	0	0	0	1	0	0	0
Right colon	6.0	0	0	1	0	0	0	0	0
Splenic flexure		0	0	1	0	0	0	0	0
Sigmoid	5.5	1	0	0	1	0	0	0	0
Rectum	6.0	2	0	0	0	1	0	0	0

TABLE 4. *Size (cm) of Villous Adenomas With Carcinoma Related to Bowel Site*

Site	Mean	4–4.9	5–5.9	6–6.9	7–7.9	8–8.9	9–9.9	10–10.9	>11
Cecum	7.6	1	2	2	0	1	2	1	1
Right colon	5.0	1	0	1	0	0	0	0	0
Sigmoid	5.5	4	3	0	0	1	0	0	0
Rectum	5.5	12	10	2	3	3	0	1	1

Dukes' stage of malignant villous adenomas was compared to the mean size, no correlation was found (Table 5). In four malignant adenomas of indeterminable Dukes' stage, mean diameter was 5.5 cm, and one villous adenoma with *in situ* carcinoma was 5 cm in diameter. Thirteen Dukes' B_1 tumors had a mean diameter of 7.6 cm, but this included two large villous adenomas of 14 and 20 cm, respectively. Ten Dukes' B_2 carcinomas had a mean diameter of 5.8 cm; one Dukes' B_3 tumor was 10 cm, one Dukes' C_2 carcinoma was 5 cm, two Dukes' C_3 tumors were 6 cm, and ten Dukes' stage D adenocarcinomas were 5.4 cm in mean diameter. Therefore, the size that a villous adenoma can attain does not appear to be significantly modified by its location in the colon or rectum. Similarly, the presence or absence of malignancy and the pathologic stage of a malignant villous adenoma clearly are not related to location of the primary adenoma nor to its size (Tables 3–5).

Discussion

Adenomas of the colon and rectum are generally regarded as premalignant lesions. Morphologically, adenomas are differentiated as either tubular, villous (papillary), or tubulovillous (villoglandular or mixed). The villous component was initially recognized as a distinct clinical entity with a significant potential for malignant transformation; the incidence of malignancy was directly proportional to size and degree of villous component.[19,20] Following the introduction of colonoscopy in 1973, the relationship between colorectal adenomas to the development of malignancy was conceptually developed.[1–11]

Though fiberoptic endoscopy is the preferred approach to the management of colonic polyps, particularly those that are pedunculated, the majority of villous and a significant number of tubulovillous adenomas are sessile. The endoscopic removal of larger sessile polyps entails increased morbidity and the increasing probability of incomplete resection with possible residual disease left behind. On the other hand, risk may outweigh benefit if the patient is subjected to a formal surgical procedure under circumstances in which there is a reasonable chance for benign disease.

Several large series have attempted to delineate criteria for further surgical intervention in adenomas with invasive carcinoma. The retrospective series by Wolff and Shinya[2] analyzed 892 endoscopically resected polyps, of which 57.3% were tubular adenomas, 29.2% were tubulovillous adenomas, and 12.4% were villous adenomas. Conversely, invasive cancer was most prevalent in villous adenomas (12.6%) followed by tubulovillous adenomas (3.8%) and tubular adenomas (3.3%). Invasive carcinomas were most frequent in larger and sessile lesions. This is a sanction confirmed by a later study by Shinya and Wolff[3] demonstrating that all gradations of cellular change from dysplasia to invasive carcinoma increased in all colon segments as the villous component of the adenoma increased. In the same series, when the villous adenoma was ≥3 cm in diameter, the incidence of carcinoma *in situ* was 33% *versus* 21.4% in tubulovillous adenomas. The incidence of in-

TABLE 5. *Size (cm) of Villous Adenoma With Carcinoma Related to Dukes' Stage*

Dukes' Stage	Mean	4–4.9	5–5.9	6–6.9	7–7.9	8–8.9	9–9.9	10–11	>11
Unknown	5.5	1	2	0	1	0	0	0	0
Dukes' A	5.0	0	1	0	0	0	0	0	0
Dukes' B_1	8.0	3	4	2	0	1	0	0	2
Dukes' B_2	5.8	4	1	0	1	1	1	0	0
Dukes' B_3	10.0	0	0	0	0	0	0	1	0
Dukes' C_1	5.0	5	4	3	0	1	1	0	0
Dukes' C_2	5.0	0	1	0	0	0	0	0	0
Dukes' C_3	6.0	0	1	0	1	0	0	0	0
Dukes' D	5.4	5	1	0	0	2	0	1	0
Total	6.1	18	15	5	3	5	2	2	2

vasive carcinoma was 13% *versus* 15%, respectively. Though polyp size was an important determinant for the presence of malignancy, invasive cancer was also found in polyps <1 cm in diameter. Furthermore, it has been recognized that adenomas with a predominantly villous component can attain large dimensions without developing invasive carcinoma.

Due to the fact that no previous studies had discriminately analyzed large colorectal adenomas with a predominantly villous morphology (greater than 60% of morphology), our study was undertaken. Based on the literature citing a significant increase in the frequency of carcinoma in villous adenomas >3–4 cm in diameter, an arbitrary lower limit of 4 cm was chosen. Of the 237 histologically documented villous and tubulovillous adenomas of the colon and rectum in a 24-year period extending from 1963 to 1987 at Roswell Park Memorial Institute, 65 cases of villous adenomas ≥4 cm were found. The incidence of invasive adenocarcinoma was found to be 85%. This is a significantly higher percentage than has been cited in the literature.[2,3,7,9,12] In comparison, Shinya and Wolff found the incidence of invasive carcinoma in villous and tubulovillous adenomas ≥3 cm to be on the order of 13–15%,[3] and Christiansen et al.[12] found a 48.5% incidence of invasive carcinoma in clinically benign villous colorectal adenomas >2 cm in diameter.[12] Muto et al.[7] reported a 46% incidence of invasive carcinoma in tubular and villous adenomas >2 cm. An incidence of invasive carcinoma of 32% was found in villous and tubulovillous adenomas >4 cm in diameter in a series of 1049 patients by Galandiuk et al.[9] In part, the high incidence of invasive carcinoma in our series may reflect the tertiary referral pattern of our institution. Another explanation may relate to the fact that a pathologist, when confronted with a colorectal surgical specimen obviously containing adenocarcinoma, directs attention to the confirmation of adenocarcinoma and may overlook or disclaim contiguous areas of benign adenoma. This may be particularly true in those larger lesions where the adenocarcinoma has overgrown the adenoma from which it initially arose. In small adenomas at an earlier stage of invasive carcinoma the predominant nature of the benign component and the transition into invasive carcinoma is more apparent.

The location of large villous and tubulovillous adenomas in our series was primarily in the right colon (28%) and the rectosigmoid (55%). A similar distribution of adenomas with a villous component has been reported in the literature,[2–16] though the frequency of cecal lesions was somewhat higher in our series. Approximately 50% of the malignant adenomas were located in the rectum, which is consistent with other studies.[9,10,12] The overall number of rectal adenomas diagnosed endoscopically remained the same before and after 1973, but four times as many cecal and right colon adenomas were noted following the introduction of colonoscopy. This may reflect a more accurate incidence of large villous and tubulovillous adenomas of the cecum and right colon, since these lesions classically are asymptomatic until they attain large size, can be readily missed by barium enema examination, and can be overlooked even by direct palpation or endoscopic examination.

In our series, 37 of 56 malignant adenomas were predominantly villous, 13 tubulovillous adenomas contained invasive adenocarcinoma, and three adenomas of each type contained both *in situ* and invasive carcinomas. In contrast, of the nine benign adenomas, four were predominantly villous and five were tubulovillous. The differentiation of the adenocarcinomas was evenly divided between well differentiated and moderately well differentiated, with only two poorly differentiated adenocarcinomas. Seventeen malignant villous and tubulovillous adenomas were noted to secrete large amounts of mucin. Five of these malignant adenomas were located in the right colon, one in the sigmoid, and 11 in the rectum. The Dukes' stage of mucin-secreting adenocarcinomas was uniformly distributed.

Seven of the 56 malignant adenomas (12%) had synchronous adenocarcinomas of the colon at the time of diagnosis. The incidence of malignancy is also directly proportional to the frequency of synchronous and metachronous adenomas.[3,9] In our series, 16 of 56 malignant adenomas (29%) were associated with 40 synchronous adenomas; the majority of these were tubular, with two containing invasive adenocarcinoma and seven containing carcinoma *in situ*. Interestingly, in virtually every instance, synchronous adenomas were found to be in the same segment of colon or rectum as the malignant primary adenoma.

Difficulty in assessing the presence of malignancy in larger polyps and the controversy regarding management of early invasive carcinomas in adenomas has led to the evolution of guidelines for management. Currently, the rationale for surgical intervention is predicated upon polyp size, sessile *versus* pedunculated, adequacy of margin, patient age, and the presence or absence of multiple synchronous or metachronous adenomas.[2,3] Further determinants also include the increased risk for carcinoma from 5–15 years for single adenomas and the male population older than 60 years of age.[15] Induration within a rectal villous adenoma has been suggested as a reliable clinical sign for the presence of invasive carcinoma.[13] Villous and tubulovillous adenomas in all segments of the colon and rectum and through all ranges in size have a known propensity to develop carcinoma. The morphology of these polyps is predominately sessile. In spite of this, several reports have advocated a conservative approach toward the management of large villous adenomas on the premise that they can be benign and that even if invasive carcinoma is present it is rarely metastatic and follows a relatively benign course.[10,11,17,21] This is contradicted by literature that demonstrates a 28–46% incidence of invasive carcinoma in villous adenomas >3 cm and a metastatic potential.[3,7,8,9,16] Furthermore, the biopsy failure rates for identifying invasive adenocarcinoma in a villous adenoma are 40–50%.[10,12]

The local recurrence rate for surgical excision alone of a villous adenoma of the colon and rectum is 17–30%,[10,12] all recurrences presenting within the first five years. The recurrence rate for villous adenomas that have been fulgurated is significantly higher and the time interval to recurrence significantly shorter. The local recurrence of a benign villous adenoma has been associated with a 7.7% incidence of subsequent malignancy.[11] However, there is a trend among endoscopists to treat villous lesions of the colon and rectum that cannot be totally removed endoscopically with electrocoagulation or laser coagulation, thus not only increasing the likelihood of local recurrence but increasing the chances of failing to recognize invasive carcinoma.

In our series of 52 malignant villous adenomas in which the Dukes' stage was determined, over 50% of the malignant villous adenomas had metastasized to regional lymph nodes or were associated with distant metastases. Half of all metastases were to visceral organs without associated lymph node involvement, raising the possibility that invasive carcinomas arising within villous adenomas do not metastasize primarily via lymphatics. For invasive carcinomas arising in rectal adenomas, seven of 32 carcinomas recurred locally within the rectovaginal septum or within the true pelvis, and another three had extension to bladder, prostate, or pelvic wall at the time of initial exploration and resection.

We speculated that although tubular and villous adenomas represent variations in an otherwise general abnormal cellular change, villous adenomas carry a higher potential for malignancy that may be biologically predetermined at an early stage in the induction and growth of the polyp. Noting that *in situ* and invasive adenocarcinomas occur in villous adenomas irrespective of size, and that some villous adenomas attain very large sizes without incurring malignancy, it is conceivable that foci of *in situ* carcinoma arise early in these polyps and are recognizable and predetermined by the time the polyp reaches a size from of 1–2 cm. This is further supported by observations that invasive carcinomas within an adenoma were confined in our series to one focus and that the coexistence of several areas of invasive carcinoma within the same large villous or tubulovillous adenoma was never observed, even after careful histologic examination of serial sections. Furthermore, the coexistence of separate foci of *in situ* carcinoma in adenomas with invasive carcinoma was infrequent. There is, of course, the possibility that separate foci of invasive carcinoma rapidly coalesce and overtake the more indolent growth of the accompanying benign component. Further studies involving careful sectioning of all adenomas with *in situ* and invasive carcinoma to determine the incidence of concomitant malignant foci would be required.

Nevertheless, it is unlikely that villous and tubulovillous adenomas simply undergo malignant transformation beyond a certain critical dimension. The contention that all adenocarcinomas of the colon and rectum arise from preexisting adenomas is also arguable. More likely is the possibility that many colorectal adenocarcinomas either are contiguous with benign components that are not appreciated by the pathologist at the time of examination of the surgical specimen, or eventually destroy any continguous benign component. Lastly, the assumption that villous adenomas in general follow a benign course and that invasive adenocarcinomas arising within these adenomas are of low grade without significant metastatic potential is not supported by our study.

Summary

In our review of 65 villous and tubulovillous adenomas ≥4 cm in diameter, 85% demonstrated a focus of invasive adenocarcinoma. The principal locations of all adenomas were in the right colon and rectosigmid region. The most frequent site of malignant tumors was in the rectum (58%), the right colon (27%), and sigmoid colon (15%). There was no relationship between size of the adenoma, location of the adenoma, or Dukes' stage. Half of all malignant adenomas demonstrated metastases to regional lymph nodes or distant metastases. Though the incidence of invasive and *in situ* carcinomas is clearly related to size of the adenoma, a linear relationship between size and incidence of malignancy could not be demonstrated in adenomas ≥4 cm. It is therefore postulated that adenomas with a predominant villous component to their morphology are biologically predetermined at an early stage in the growth of the neoplasm to manifest cellular changes capable of leading to malignancy. Otherwise, the neoplasm retains the capacity to attain large dimensions without ever incurring malignancy.

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The Management of Penetrating Injuries of the Back

A Prospective Study of 230 Patients

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This is a prospective study of 230 patients with penetrating injuries of the back. The decision to operate or observe was taken exclusively on the abdominal physical findings. One hundred ninety-five patients (85%) did not require operation, 30 (13%) underwent a therapeutic laparotomy, four (1.7%) an unnecessary operation, and one patient (0.4%) had a completely negative laparotomy. The diagnosis and management was delayed in five (2.2%) patients with no serious consequences. Mortality rates were not recorded in this series. The initial physical examination was accurate in 95.2% of the patients. We suggest that penetrating injuries of the back should be assessed in the same way as anterior abdominal injuries. Physical abdominal examination is reliable in detecting significant intra-abdominal injuries.

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WE HAVE PREVIOUSLY SHOWN that many anterior abdominal penetrating injuries can safely be managed exclusively on abdominal physical examination. Evisceration, paracentesis positive for blood, free air under the diaphragms, and shock on admission are not absolute indications for surgery.[1,2] Penetrating wounds in the back are generally considered as a distinct form of abdominal trauma.[3] The vertebral column and the thick musculature provide a better protective barrier than the anterior abdominal wall, and retroperitoneal injuries may not be clinically detectable in the early stages. In the present study we report our experience with this type of trauma.

Patients and Methods

A prospective study over a 15-month period (1986–1987) took place in three of five surgical units at Baragwanath Hospital, Johannesburg. The back was defined as the area between the tips of the scapulae, the iliac crests, and both midaxillary lines. Patients with superficial wounds, as shown by digital exploration, were not included in the study.

Patients with signs of an acute abdomen (severe tenderness, guarding, or rebound tenderness) were operated on immediately. Patients with no abdominal signs or minimal ones (mild, local tenderness) were chosen for conservative management. Following physical examination (which included auscultation of the renal regions for a bruit) erect chest and abdominal x-rays were taken, and urine was tested for blood. In the presence of a bruit or gross hematuria an intravenous pyelogram (IVP) was done. A renal arteriogram was obtained if the kidney was not visualized on IVP. All patients had a nasogastric tube inserted and were put on hourly blood pressure and pulse checkings for 24 hours. The abdomen was assessed clinically every 3 to 4 hours. No prophylactic antibiotics were given, except in the presence of an intercostal drain for an associated hemopneumothorax. If signs of peritonitis developed, an operation was carried out; otherwise, the patients were discharged, usually in 2 to 3 days.

Results

There were 230 patients (202 men and 28 women) with a mean age of 26 years. Twenty-three per cent of the patients had multiple wounds in the back. The weapon was a knife in 97% of the cases, and a gun in 3%. The victims reached the hospital in a mean time of 90 minutes after the injury.

Initial Assessment

Thirty-five patients (15.2%) had signs of an acute abdomen on admission and were operated on immediately. The remaining 195 (84.8%) were selected for observation. Microscopic hematuria was present in 57 (25%) and gross hematuria in 8 (3.5%) patients. An IVP was obtained only in the 16 patients with gross or 4+ hematuria on dipstick, and abnormalities were demon-

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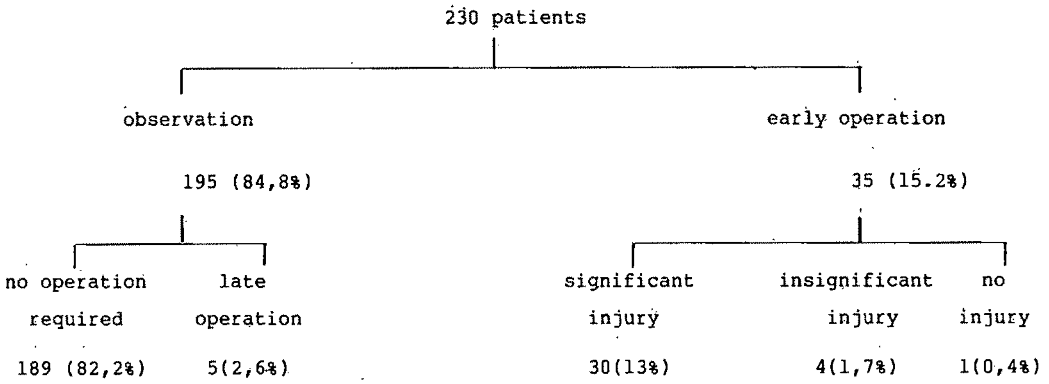

FIG. 1. Management of 230 patients.

strated in four patients. However, the IVP did not directly influence the emergency management in any of our patients. An abdominal x-ray was obtained in all patients, but it was diagnostic in only six cases (2.6%) where it showed free air under the diaphragm. Five patients had signs of an acute abdomen, and they would have been operated on irrespective of radiologic findings. The most common associated injury was a hemopneumothorax (32% of the patients) followed by a head injury (6%).

Results of Treatment (Fig. 1)

Of the 35 (15.2%) patients who were operated on immediately 30 (13%) had serious intra-abdominal injuries requiring repair, 4 (1.7%) had nonsignificant injuries (*i.e.*, retroperitoneal hematomas, small liver lacerations), and one (0.4%) had a completely negative laparotomy. The injured viscera in the patients with a positive celiotomy included nine colons, five kidneys, five diaphragms, four small bowel, two livers, two stomachs, two spleens, and one pancreas. No mortality rate or significant intra-abdominal complication was recorded in the group of patients who underwent an early operation. The average hospital stay was 7 days.

In the group of 195 (84.8%) patients who were initially selected for observation, five (2.2%) developed signs of peritonitis and were operated on, but retrospectively the operation was necessary in only four (1.7%). Another patient developed a bruit over the kidney and a false aneurysm was diagnosed on angiography. A partial nephrectomy was performed (Table 1). There was no mortality rate, but there was one pancreatic fistula that closed spontaneously. In the remaining 190 patients who were managed nonoperatively there was no mortality rate. The average hospital stay was 2.4 days. One patient was readmitted 8 weeks after discharge with a right subdiaphragmatic abscess that was drained percutaneously.

Discussion

The assessment of penetrating injuries of the back is generally considered more difficult than assessment of injuries of the anterior abdomen. The confinement of the damage to the retroperitoneum may result in delay of the diagnosis and management of a serious injury. Missed colonic or duodenal perforations may prove catastrophic. For these reasons concern has been expressed about the safety of conservative management of penetrating wounds of the back.

Routine exploration is associated with an unacceptably high incidence of unnecessary operations. The thick musculoskeletal wall of the back provides a good protective barrier to the intra-abdominal structures. In this study only 34 patients (14.8%) had a significant intra-abdominal injury requiring surgical intervention. Other series reported similar findings.[4,5] In anterior abdominal wounds this figure is 52%.[1] A negative laparotomy performed under emergency conditions, often by junior staff, poses significant risks. Because of these problems, most trauma centers apply some form of selective conservative management. Physical examination, local exploration of the wound for peritoneal penetration, peritoneal lavage, and sophisticated contrast-enhanced CT enemas have all been used to identify the patients requiring surgery.

The diagnostic accuracy of the initial abdominal physical examination has been reported to be between 72 and 92%.[3,4,6] Our experience has demonstrated reliability with an overall accuracy of 95.2% (false-positive, 2.6%; false-negative, 2.2%). We have reported similar results for anterior abdominal wounds (651 patients: overall accuracy, 94%; false-positive, 3.2%; and false-negative, 2.9%) (Table 2).[1] We attribute our high accuracy to three factors: (1) selective conservatism has been extensively used at our hospital for more than 25 years;

TABLE 1. *Five Late Operations*

Delay	Operative Findings	Complications	Hospital Stay (d)
36 h	Pancreatic injury	Fistula	25
48 h	Retroperitoneal hematoma		6
4 h	Small bowel		7
6 h	Colon (primary repair)		7
10 d	Renal aneurysm (partial nephretomy)		7

TABLE 2. *Accuracy of Physical Examination in Anterior and Posterior Abdominal Wounds*

	No. of Patients	False-positive Initial Physical Examination (%)	False-negative Initial Physical Examination (%)	Accuracy of Physical Examination (%)
Anterior abdominal wounds	651	3.2	2.9	93.9
Posterior abdominal wounds	230	2.6	2.2	95.2

* Demetriades and Rabinowitz.[1]

(2) we see large numbers of patients with penetrating trauma; and (3) experienced surgeons are always present on a 24-hour basis.

Local exploration of the wound has been used as a screening method for identifying patients requiring surgery.[6] However, exploration through the thick musculature of the back is a difficult task. Furthermore, deep penetration does not mean serious intra-abdominal injury. We have shown that 30% of the patients with proven peritoneal penetration do not have significant intra-abdominal injuries requiring surgery.[1]

Peritoneal lavage has been advocated in the assessment of these patients.[3,4,6] We believe that lavage has no place in the management of penetrating injuries of the back. If the injury is confined in the retroperitoneum, the lavage will be falsely negative. A lavage positive for blood is not an absolute indication for surgery. Free blood may have originated from the abdominal wall wound or from a superficial liver laceration. We have shown that many penetrating liver injuries can be managed nonoperatively.[7] The dangers associated with peritoneal lavage in the presence of a colonic perforation cannot be overemphasized.

Phillips et al.[4] used contrast-enhanced CT enemas to detect significant visceral or vascular injuries. The procedure includes a gastrographin meal, a gastrographin enema, and intravenous diatrizoate, combined with an abdominal CT scan. This expensive and time-consuming investigation had a yield of less than 2%, and there is no data to support that it detects small retroperitoneal perforations of the colon or duodenum. Further assessment of this technique is necessary.

The value of the plain abdominal x-ray seems to be very limited. We have a positive yield of 2.6%, and in no case did the radiologic findings directly influence the decision to operate or observe. Free air under the diaphragm is not in itself an absolute indication for operation. Although these cases are assessed with great caution, the final decision to observe or operate is taken exclusively on the abdominal physical examination. The free intraperitoneal air may have originated from outside through the abdominal wound or from an associated right pneumothorax with perforation of the right diaphragm.

We have previously reported 16 such patients treated conservatively.[1] Chest x-rays are essential in the diagnosis of a hemopneumothorax or diaphragmatic injuries. An elevated left diaphragm or suspicion of viscus in the chest should be further investigated by means of screening, contrast studies, or laparoscopy in the appropriate cases. The role of the IVP in the assessment of penetrating injuries of the back is not clear. Some authors recommend routine IVP irrespective of urinalysis.[3] Others reserve this investigation for patients with microscopic or gross hematuria. We perform IVPs only for wounds over the kidneys associated with gross hematuria or 4+ hematuria on dipstick. Coppa et al.[3] recommended exploration of all penetrating renal injuries. We reserve operative intervention only for pedicle injuries or uncontrollable hemorrhage. Any other kidney injuries are managed conservatively. Follow-up of these patients for late development of false aneurysms or arteriovenous fistule is imperative.

In conclusion, we believe that penetrating injuries of the back should be assessed in the same way as those of the anterior abdomen. Physical abdominal examination is reliable in detecting significant intra-abdominal injuries. There is no need for any special diagnostic procedures except for a chest x-ray, urinalysis, and an IVP in the appropriate cases.

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Relationship of Estrogen and Progesterone Receptors to Prognosis in Breast Cancer

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To ascertain the role of estrogen (ER) and progesterone (PR) receptors as prognostic indicators of resectable breast cancer, the records of 204 patients were analyzed whose receptor studies were done at the Maimonides Medical Center from 1975 to 1983. All patients had radical or modified radical mastectomies and did not show any evidence of distant metastases at the time of operation. Median follow-up was 37 months. An additional 117 patients received some form of adjuvant therapy, mainly chemotherapy, and were analyzed separately. Life table analysis using the log rank test for measuring significance, and a Cox multivariate analysis was performed. At 48 months, 22% of the ER positive (ER+) group *versus* 33% of the ER negative (ER−) group had recurred as compared to 16% and 35% for the PR+ *versus* PR− groups, respectively. Life table analysis of the disease free interval (DFI) showed that the difference between the ER+ and ER− groups was not significant ($p > 0.1$), while the difference in DFI between the PR+ and PR− groups was significant ($p < 0.05$). Multivariate analysis revealed that the most important factors in predicting the DFI were nodal status ($p < 0.001$), tumor size ($p < 0.025$), and progesterone receptor status ($p < 0.05$). Estrogen receptor status was not found to be significant. In conclusion, PR− patients have a shorter DFI than PR+ patients and that PR status is a more valuable predictor of DFI than ER status.

THE IMPORTANCE of hormonal receptors in predicting the likelihood of response to hormonal manipulation in patients with metastatic breast cancer is well established.[1] Patients who are hormone receptor-positive are likely to respond to a variety of hormonal treatments whereas receptor-negative patients virtually never respond. This probably accounts for the longer survival of receptor-positive patients.

Less clear, however, is the possible influence of hormonal receptors on the likelihood of remaining disease free. Most early studies on this subject focused on the estrogen receptor content. Progesterone receptor measurement did not enter routine clinical practice until the late 1970s, and the relationship between the PR and prognosis is less well studied. Since Horowitz and McGuire first proposed the value of the progesterone receptor as a clinical tool, attention has been focused at defining its utility as a predictor of prognosis.[2]

There is a controversy in the literature regarding the value of estrogen receptors in predicting the disease free interval (DFI).[3-9] This variance in the literature may be due to several factors including differences in laboratory methodology and standardization, variations in study entry criteria regarding stage and primary treatment modalities, and statistically insignificant study samples or follow-up periods.

Another significant methodologic difference is the inclusion in many published series of patients who have received hormonal and/or cytotoxic adjuvant therapy. Adjuvant therapies have been shown to prolong the DFI in various subsets of patients.[10-13] Thus, the inclusion of a significant fraction of patients who received adjuvant therapy in all probability bias any evaluation of the predictive value of hormonal receptors on the natural history of surgically treated breast cancer.

The present report analyzes a series of 204 patients who were not treated with any adjuvant therapy, eliminating this confounding variable. We analyzed the effects of estrogen and progesterone receptors on the DFI and sought to identify other factors that might have an impact on the prognosis of breast cancer.

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† Deceased.

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TABLE 1. *Patient Characteristics*

Total no. of patients	204
Age (yr)	
Average	63
Median	65
Menopausal status (%)	
Premenopausal or perimenopausal	18
Postmenopausal	82
Median follow-up (mo)	
All patients	37
Disease free patients	43
Stage	
Stage I	69 (34%)
Stage II	100 (49%)
Stage III	35 (17%)

Methods

Estrogen receptor determinations have been performed in our laboratory since 1974 and progesterone receptors since 1975. Between 1975 and 1977 the sucrose density gradient method was used, and later replaced by dextran-coated charcoal. The assay was considered negative if <3 fmol of receptor protein/mg of cytosol protein was present; borderline was determined at 3–10 fmol and positive for >10 fmol. For the purpose of this study all borderline values were considered positive. The technique of receptor analysis is described elsewhere.[14]

All patients in this study had localized breast cancer and underwent either a radical or modified radical mastectomy. Receptor studies were done on the primary tumor. Any patient who had evidence of metastatic disease at the time of surgery or previous breast malignancy was excluded. A total of 321 patients satisfied the above criteria and were available for analysis. Of these, 117 received some form of adjuvant therapy and were analyzed separately. A total of 204 patients remained, and they constitute the basis of this report.

For the purposes of this study adjuvant therapy is defined as any postoperative treatment: hormonal, cytotoxic, and/or radiation therapy. No attempt was made to differentiate among these groups since the subgroups were too small for any meaningful analysis.

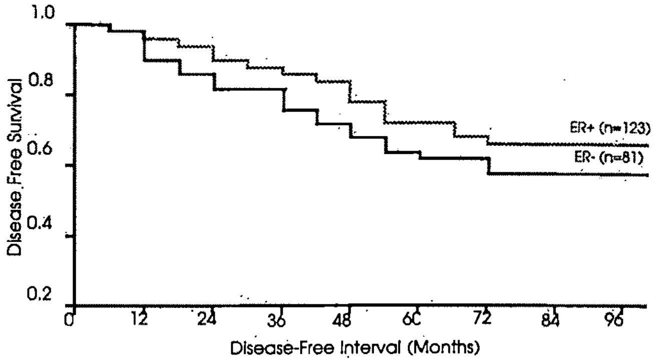

FIG. 1. Life table analysis of ER+ *versus* ER− ($p > 0.1$). Only patients not receiving adjuvant therapy are included.

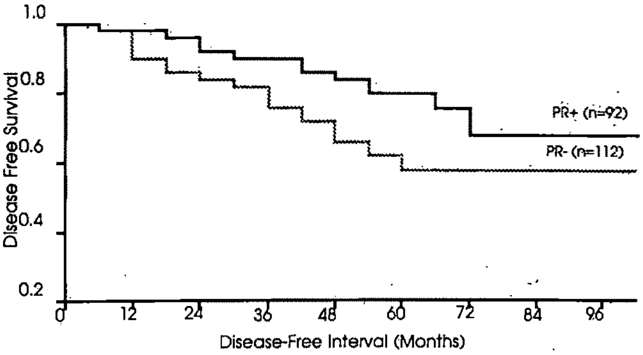

FIG. 2. Life table analysis of PR+ *versus* PR− ($p < 0.05$). Only patients not receiving adjuvant therapy are included.

The date of recurrence was the date of clinical detection of recurring tumor. Follow-up data was obtained from hospital and clinic records and from attending physicians.

Life table analyses were performed using standard actuarial methods. Differences between curves were analyzed using the log rank test for censored survival data. Cox's partially nonparametric regression model was used to evaluate the contribution of various factors in the prediction of the DFI.[15] Computations were performed with SAS computer programs release 82.3.

Results

Table 1 presents patient characteristics. It should be noted that a high percentage of our patients are postmenopausal, a patient group more likely to have a positive hormonal assay.

After 48 months, 8% of stage I patients had recurred *versus* 22% and 60% for stages II and III, respectively. This increased to 21%, 33%, and 70%, respectively, for those patients with 72 month follow-up. In all instances, these differences were significant ($p < 0.01$). The recurrence rate at 48 months for the ER+ *versus* ER− group was 22% *versus* 33%, respectively, while for the PR+ *versus* PR− group it was 16% *versus* 35%, respectively.

Figure 1 compares the ER+ *versus* ER− groups. The ER+ group showed a longer DFI, but this trend was not statistically significant ($p > 0.1$). Figure 2 shows the life table comparison of PR+ *versus* PR− patients. This difference was significant ($p < 0.05$).

Table 2 reports the results of hormonal receptor determinations.

The group of 117 patients who received some form of adjuvant therapy were included in the study group and

TABLE 2. *Receptor Values*

ER+	123 (60%)
ER−	81 (40%)
PR+	92 (45%)
PR−	112 (55%)
ER+/PR+	82 (40%)
ER+/PR−	41 (20%)
ER−/PR+	10 (5%)
ER−/PR−	71 (35%)

the life table analysis was repeated. Again, the difference between the ER+ and ER− groups was not found to be significant ($p > 0.1$), while the difference between the PR+ and PR− groups was significant ($p < 0.025$). The life tables for estrogen and progesterone are shown in Figures 3 and 4, respectively.

A Cox multivariate analysis was performed to measure the significance of each of the following factors: nodes (0 vs. 1-3. vs. >3) $p < 0.001$, tumor size (T_1 vs. T_2 vs. T_3), $p < 0.025$, progesterone receptor (+ vs. −) $p < 0.05$, estrogen receptor (+ vs. −) $p > 0.25$, age, $p > 0.5$, and adjuvant therapy (yes vs. no) $p > 0.25$. These factors are listed in Table 3. These results show that PR positivity, independent of all other factors, is a significant determinant of the DFI. This is not so for the estrogen receptor.

Discussion

The finding of an insignificant difference between the estrogen positive and negative groups is not unexpected and has been reported previously. Kinne et al.[4] found only borderline ($p = 0.06$) significance after 14 months of follow-up despite a very large series containing 1034 patients. Hilf et al.[5] and Skinner et al.[7] also did not find a significant difference. The majority of studies, however, do show a difference.[6,8,9] Wide variation in patient population size, length of follow-up, and the inclusion of patients who received adjuvant therapies are among factors likely to be responsible for the divergent results.

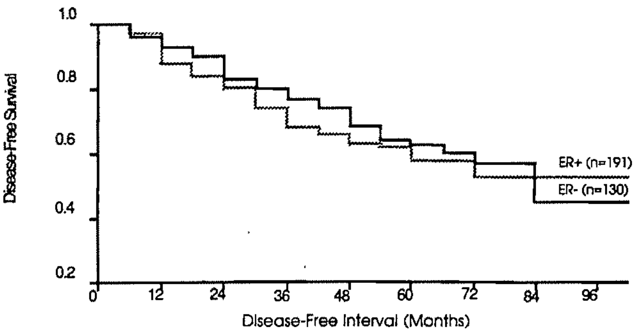

FIG. 3. Life table analysis of ER+ *versus* ER− ($p > 0.1$). Patients receiving adjuvant therapy are included.

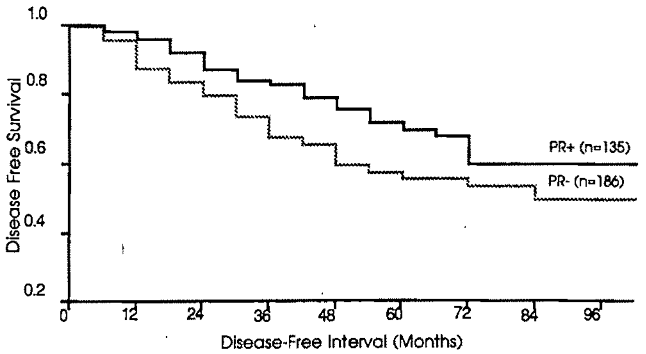

FIG. 4. Life table analysis of PR+ *versus* PR− ($p < 0.025$). Patients receiving adjuvant therapy are included.

The potential value of the progesterone receptor content has not been studied as extensively as the estrogen receptor. Published data suggest that it is at least equal to if not better than the estrogen receptor for predicting the DFI.[8,16] In this study the progesterone assay was a more sensitive indicator of recurrence potential of the tumor. In addition, the results of the Cox regression analysis indicated that unlike progesterone, estrogen was not a significant independent predictor of the DFI when all the other factors are controlled.

In a recent study, Clark et al.[8] analyzed 189 patients with stage II disease using similar statistical methods. Their patient group differed from those in the present study in that all patients had received adjuvant chemotherapy and two out of three had received tamoxifen. Median follow-up was 32 months. Significant differences in the DFI were found using life table analysis of the data subdivided according to either estrogen or progesterone receptor content. Despite these life table findings, analysis using the Cox multiregression model showed that estrogen receptor was not a significant independent variable. Thus, the study by Clark et al.[8] and ours both show that once the other factors in the regression analysis are known, namely, nodal status, tumor size, and progesterone receptor content, the knowledge of the estrogen receptor content is of little additional help in predicting the DFI. Our data also extend these observations to a group of patients treated solely by primary surgery without adjuvant therapies.

TABLE 3. *Factors Considered in the Multivariate Model*

Factor	p Value
Nodes (0 *vs.* 1-3 *vs.* >3)	<0.001
Tumor size (T_1 *vs.* T_2 *vs.* T_3)	<0.025
Progesterone receptor (+ *vs.* −)	<0.05
Estrogen receptor (+ *vs.* −)	>0.25
Age	>0.5
Adjuvant therapy (yes *vs.* no)	>0.25

Treatment with tamoxifen, with or without cytotoxic chemotherapy, has been shown to prolong the DFI of postmenopausal patients who are ER+.[10,13] Cytotoxic chemotherapy has been convincingly demonstrated to prolong the DFI of premenopausal patients without apparent regard to hormonal status.[11,12] Whether chemotherapy exerts a significant effect in postmenopausal patients is still debated.[17] Thus, the effect of adjuvant therapy on the DFI can be difficult to predict and will likely exert dissimilar effects on various subsets. For example, Lippman et al.[18] reported that ER+ tumors respond less well to adjuvant therapy than ER− tumors. Kiang et al.[19] and others,[20,21] however, have come to the opposite conclusion. Others have not found any relationship or have found a relationship only in premenopausal women.[5,22,23] Regardless of the effect on specific subsets, adjuvant therapy is likely to confound the evaluation of the relationship of receptor status on the natural prognosis of breast cancer.

With the widespread implementation of adjuvant treatments, especially chemotherapy, commencing in the late 1970s, adequate study of the natural history of breast cancer relative to hormonal receptors became increasingly difficult. In contrast to other reported series, the current group of patients consists entirely of patients who never received postmastectomy treatment. Our laboratory began to analyze hormonal receptors in 1974, thus affording us an opportunity to evaluate the potential prognostic significance of estrogen and progesterone receptors in a cohort of patients treated with mastectomy alone. The homogeneity of the group with regard to treatment removes adjuvant therapy as an additional confounding variable, a problem that hampers evaluation of a number of published series.

Knowledge of the relationship of hormonal receptor status and the natural history of the disease is of some importance in patient management after primary surgery. Conventionally, adjuvant chemotherapy is withheld from stage I patients. It has been suggested that there is a subgroup of patients at high risk for early recurrence who may well be candidates for treatment. Among the proposed high risk criteria is receptor negativity.[24,25] Our study supports this view, especially with regard to the progesterone receptor.

In the present study the inclusion of our adjuvant therapy group in the life table analysis did not alter the results (Figs. 3 and 4). The difference in the DFIs remained significant in the PR+ *versus* the PR− groups. However, patients treated with adjuvant therapy did worse than those not so treated. Presumably, this is a patient selection artifact since patients with more advanced disease were more likely to be treated with adjuvant therapy. Fifty per cent of stage III patients had adjuvant therapy whereas only 12% of those with stage I were so treated. In addition, those patients entering the study at a later date were more likely to have adjuvant therapy. This is also supported by the lack of significance of adjuvant therapy in the regression model. In essence, the decreased DFI observed in the adjuvant group can be attributed to changes in the other significant factors of the model, namely, nodal status, tumor size, and progesterone. It must be cautioned that this study was not designed to analyze adjuvant therapy, and no conclusions can be drawn from these data about its efficacy.

Thus, this study confirms that the progesterone receptor is a valuable indicator of the recurrence potential in breast cancer, independent of estrogen receptor positivity and treatment with adjuvant therapies.

Acknowledgment

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Host and Tumor Responses to Varying Rates of Nitrogen Infusion in the Tumor-bearing Rat

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The influence of variations in nitrogen content of nutritional substrate available to the tumor-bearing (TB) host on tumor growth and host have not yet been completely defined. One hundred fifty-two growing Fischer 344 rats were either transplanted with a sarcoma (TB) or injected with saline (NTB, day 0), had aseptic placement of superior vena cava catheter (day 14), and were infused with total parenteal nutrition solutions (days 18–28). Isocaloric solutions (approximately 50 kcal/d) contained either 0%, 5%, 16%, 33%, 67%, 100%, 133%, or 167% of normal intake of an adequate amino acid mixture. Final tumor weight in the 5% group (23.4 ± 3.0 g) was significantly less than tumor weights of all other groups (range: 33.3 ± 3.3 to 42.6 ± 11.3) ($p < 0.05$). The carcasses of TB animals were slightly smaller than NTB animals but showed no major alterations in protein, fat, or water composition. This study suggests that the tumor can be starved selectively by strictly nutritional means with complex accompanying host carcass and organ changes.

OPTIMUM NUTRITIONAL SUPPORT for the tumor-bearing (TB) host remains undefined. Numerous controlled clinical trials of standard intravenous (I.V.) hyperalimentation with a variety of tumor types and under a variety of treatment conditions have revealed little evidence of patient benefit.[1,2] The sole exception is a trial of I.V. hyperalimentation given before operation to patients with upper gastrointestinal malignancies, which demonstrated decreased postoperative morbidity and mortality rates.[3]

Experimental work in inbred rats with transplantable tumor systems has also failed to reveal significant host benefit with aggressive nutritional support.[4-15] Further, tumor growth stimulation out of proportion to host carcass support has been demonstrated in most tumor-rat systems in which it has been carefully examined.[4-10] One clinical study in head and neck cancer patients[16] and one study of colorectal cancer patients also suggest similar tumor stimulation in man.[17] The vast majority of controlled clinical data can be interpreted as showing that little benefit to the host and possible detriment from tumor stimulation result from aggressive nutritional support.

These data all suggest that nutritional approaches other than standard balanced nutritional solutions should be explored in an attempt to find a nutritional therapy that would benefit the host while being detrimental to the tumor. Several studies with conflicting results have been undertaken in which fat was exchanged for carbohydrate as the basic energy source.[8,11] In our study the response of a rat-tumor system to isocaloric variation in total nitrogen infusion over a range of 0–167% of normal has been systematically evaluated. The results suggest that low levels of nitrogen infusion selectively starve the tumor.

Methods

Experimental Design

Male Fischer 344 rats of approximately 150 g were acclimated to the laboratory and a synthetic casein-based diet[18] for three days. TB rats were randomly selected to undergo tumor transplantation with 1×10^6 methylcholanthrene-induced tumor cells. The origin of this tumor, methods for preparing and checking the viability of single cell suspensions, and the natural history of tumor growth in rats of this size have been described in detail.[19] Rats selected as nontumor-bearing (NTB) control animals were anesthetized with pentobarbital (30 mg/kg) in the same manner as TB animals but were injected with 0.5 mL of a sterile saline solution. Following either tumor inoculation or saline injection on day

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0, rats were allowed to resume the casein diet on an *ad libitum* basis for 14 days.

On the 14th day the rats were again anesthetized with pentobarbital (30 mg/kg) and had aseptic placement of superior vena cava catheters, which were sterilely connected through flexible spring catheter shields to the tops of metabolic cages.[20] The system was kept patent with a daily injection of 1.0 mL of heparinized saline (10 U/mL) for the next 4 days. The 4-day period was selected to allow rats to recover completely from the stress response to the operation.[20,21]

Nutritional Support

On day 18 of the experiment, rats were randomly allocated to groups to begin a 10-day period of nutritional support with total parenteral nutrition (TPN) solutions of varying nitrogen content. The nutritional solutions had mineral, fat, and vitamin contents that have been documented to support normal growth of these rats over a 21-day period.[18] The nitrogen content consisted of a balanced amino acid mixture with the same ratio as that derived from hydrolized casein.[22] The quantity of amino acids in the solutions was 0%, 5%, 16%, 33%, 66%, 100%, 133% and 167% of normal nitrogen intake.[18] The glucose content of each solution was adjusted to make all of the experimental solutions isocaloric. The amino acid mixture was assumed to have 4.00 kcal/g, and the anhydrous glucose (Sigma Chemical Co., St. Louis, MO) was assumed to have 3.74 kcal g. Additional control groups of rats consisted of one group (CON) of both TB and NTB rats, which were killed on day 18 of the experiment, and groups of TB and NTB orally fed control rats, which were allowed to eat *ad libitum* a solid amino acid-based diet (AAD),[18] which was nearly identical to the diet infused nutritionally in the 100% group of TPN rats.

Evaluation of Results

On days 18, 21, 23, 25, and 28 of the experiment, rat weights and tumor dimensions were determined. The total weights of nutritional solutions infused and solid diet ingested were also measured over this 10-day period. On day 28, rats were killed by injection of an overdose of pentobarbital anesthesia. TB rats had the tumors excised and weighed. Blood was collected for determination of hematocrit, white blood cell count, and differential count. The gastrointestinal tracts were opened and all undigested food and stool was collected and weighed. Carcass weights were determined by subtracting tumor weight and gastrointestinal tract content weight from total body weight for TB rats and gastrointestinal tract content weight from total body weight for NTB rats. Complete postmortem examinations were performed. No evidence of metastatic tumor was detected in any animal. The heart, lungs, stomach, small intestine, colon, liver, spleen, and testes were all dissected free, cleansed of fat, and weighed.

All of the viscera were then frozen with the entire rat carcass including the skin for later carcass composition analysis for total water, fat, and protein content. Tumors were similarly frozen for composition analysis. The details of these analytic procedures have been described previously.[4,5,18] Briefly, the carcasses were cut into small pieces and autoclaved at 220 C for 15 minutes to soften the pelts. They were homogenized in 1 L of water using a high-speed homogenizer. Aliquots (approximately 200 g) of the homogenate were then freeze-dried for 1 week until a stable weight was reached. The final weight of dry material in the aliquot allows calculation of the total quantity of dry material in the original carcass. Subtraction of this from the total carcass weight yields the total body water content. The dry material was then analyzed for total nitrogen content using 0.5 g samples and a macro-Kjeldahl technique. It was also analyzed for total fat content with a petroleum-ether extraction. The weight of total dry material in the rat and the fat content per gram and nitrogen content per gram allows calculation of total fat and nitrogen in the original carcass. Multiplication of total nitrogen by 6.25 yields a total protein content. Tumor composition is determined in a similar manner. These independent analyses routinely account for 94–96% of rat carcass and 98% of tumor weight.[4,5,18,24] These results are consistent with body composition data, which indicate that approximately 5% of total carcass is skeleton that is not in water, protein, or fat compartments.

Distributions of Rats into Groups and Calculations

Initially, rats were randomly assigned to nutritional groups ranging from 33% to 167% of normal nitrogen intake and the CON and AAD groups. Six rats were placed in each TB group and five in each NTB group. Preliminary analysis of the results suggested little influence on tumor growth from variations of nitrogen intake over these ranges. Additional groups of animals were then tested at the 16%, 5%, and 0% levels. These results suggested that tumor growth might be inhibited at the lower ranges. Because these latter results were obtained with groups that were not a part of the original randomization, it was decided that additional animals should be tested at these lower ranges with concomitant randomization of TB animals to the 66% and 100% groups. Additional animals were also initially placed in TB-133 and TB-167 groups because rats in these groups tended not to survive the final 10 days of the experiment. The final number of animals starting in each ex-

TABLE 1. *Nitrogen Intake, Caloric Intake, and Rat Survival During Ten Days of Nutritional Support*

	TB Rats				NTB Rats			
Nutritional Group	n Day 18	N Intake (mg N/d)	Caloric Intake (kcal/24 h)	n Day 28	n Day 18	N Intake (mg N/24 h)	Caloric Intake (kcal/24 h)	n Day 28
005	10	22.6 ± 0.4*	48.4 ± 0.4	10	8	22.1 ± 0.6	47.8 ± 0.8	8
016	9	68.8 ± 0.7	47.2 ± 0.5	9	8	67.1 ± 0.9	46.0 ± 0.7	8
033	6	139.4 ± 2.5	48.0 ± 0.9	6	5	140.7 ± 1.2	48.5 ± 0.4	5
066	11	284.1 ± 4.2	48.3 ± 0.7	11	5	279.2 ± 8.8	47.4 ± 1.5	5
100	11	431.8 ± 3.8	49.1 ± 0.4	11	5	432.0 ± 3.1	49.1 ± 0.3	5
133	7	575.3 ± 4.1	49.2 ± 0.4	2	5	563.3 ± 16.1	48.2 ± 1.3	5
166	8	737.7 ± 8.5	50.2 ± 0.6	3	5	731.1 ± 3.8	49.8 ± 0.3	5
CON*	6	0.00	—	—	5	0.00	—	—
AAD†	6	330.1 ± 44.3	42.1 ± 5.7	6	5	420.8 ± 22.1	53.7 ± 2.8	5

Values are given as mean ± SEM.
* Rats killed day 18.

† AAD = orally fed *ad libitum* a complete amino acid diet.
n = number of rats in group.

perimental group is indicated in Table 1. Since the basic trends observed in the first analysis of the 0%, 5%, and 16% group were observed in the second experiment with these groups, all of these data have been combined and analyzed as a single experiment.

Mean values and SEM were calculated for all of the variables studied. Mean values were initially compared with an analysis of variance.[23] Correlation coefficients and regression analysis were used to analyze data from TPN groups in which nitrogen intake was varied.[23]

Results

Rat Survival and Nutrient Intake

A total of 152 rats began the experimental protocol. Twenty-two rats (12 TB and 10 NTB) failed to complete the 28-day experiment for mechanical or infectious reasons (catheter infiltration, catheter disconnection, or catheter infection as determined by postmortem examination).[20] Five attempts to support TB rats through the 10 days of nutritional supplementation with 0% nitrogen all resulted in animal deaths between the 23rd and 25th experiment days. Only two of seven TB-133 rats and three of eight TB-166 rats survived until day 28. None of these deaths could be related to mechanical or infectious problems, and all occurred between days 25 and 28 of the experiment. All data from the 22 animals having mechanical or infectious failure and the five 0% animals have been excluded from further consideration. Tumor weight calculations from the 15 TB-133 and TB-167 rats who survived until day 25 have been included. The final numbers of rats completing the study and their nutrient intakes are illustrated in Table 1.

There were no significant differences in the caloric intakes of the infused rats. The differences in nitrogen intake were significantly different ($p < 0.001$). Both the caloric and nitrogen intake of the TB-AAD rats were significantly less than the NTB-AAD rats ($p < 0.001$).

Blood and Organ Weight Changes

All TB rats except the control rats were anemic with hematocrits ranging from 23.6 ± 2.6% to 32.7 ± 3.4%. These hematocrits were significantly different ($p < 0.05$) than the TB-CON rats and all of the NTB rats where hematocrits ranged from 39.0 ± 0.6% to 48.7 ± 2.7%. White blood cell counts were elevated in all TB groups except for TB-CON and ranged from 12.7 ± 1.1 to 22.8 ± 2.4 $(\times 10^3/\text{mm}^3)$. The TB-CON and all of the NTB group means ranged from 5.9 ± 1.6 to 10.5 ± 0.8 $(\times 10^3/\text{mm}^3)$. These increased white blood cell counts could be attributed to polymorphonucleocytes, which ranged from 56.7 ± 11.4% to 71.0 ± 2% in the TB groups and 20.0 ± 3.2% to 52.0 ± 3.3% in the TB-CON and NTB series.

A complex group of interrelationships between organ weight, changes in nitrogen infusion, oral *versus* I.V. nutritional support, and TB or NTB status was observed. Liver, heart, and kidney weights all increased linearly with rate of nitrogen infusion (Fig. 1). TB groups had mean organ weights greater than NTB groups at each level of infusion for these three organs. TB rats receiving the AAD had significantly smaller livers than NTB rats ($p < 0.05$). There were no differences in heart or kidney weights between TB and NTB rats receiving the AAD. The stomach, small bowel, and colon weights demonstrated a nonlinear tendency to be lowest at the 5% and 16% rates of nitrogen infusion (Fig. 2). NTB animals had elevated stomach weights when compared to TB animals at all levels of infusion. No difference in TB and NTB rats was demonstrated in small bowel or colon weights. Free-feeding TB and NTB rats eating the AAD had markedly higher stomach and small bowel weights when compared to rats receiving nutrients by TPN infusion. Free-feeding NTB rats had greater stomach and small bowel weights than TB rats. Spleen weights were lowest in the low nitrogen infusion

TB and NTB groups (Fig. 3). They increased in a nonlinear fashion with increasing levels of nitrogen infusion, with TB rats developing much larger spleens than NTB rats at high rates of nitrogen infusion. Lung weights were lowest in the 5% and 16% infused groups. No other discernible patterns were evident in lung or testes weights (Fig. 3).

Carcass Weight and Composition Changes

There were no significant differences in mean total body weights among all groups of animals on either day 0, day 14, or day 18. Day 28 total body weights varied directly with the rate of nitrogen infusion for TB rats (r = 0.55, p < 0.001) and for NTB rats (r = 0.70, p < 0.001, Fig. 4). Total body weights of TB rats were greater than for NTB rats (Fig. 4). Examination of carcass weights (carcass weight = total body weight − tumor weight − gastrointestinal content) revealed similar patterns of weight with regard to rate of nitrogen infusion (TB: r = 0.40, p = 0.003; NTB: r = 0.69, p < 0.001). Carcass weights of TB animals tended to be lower than NTB animals (Fig. 4). The day 28 total body weights of TB-AAD rats were similar to the day 28 total

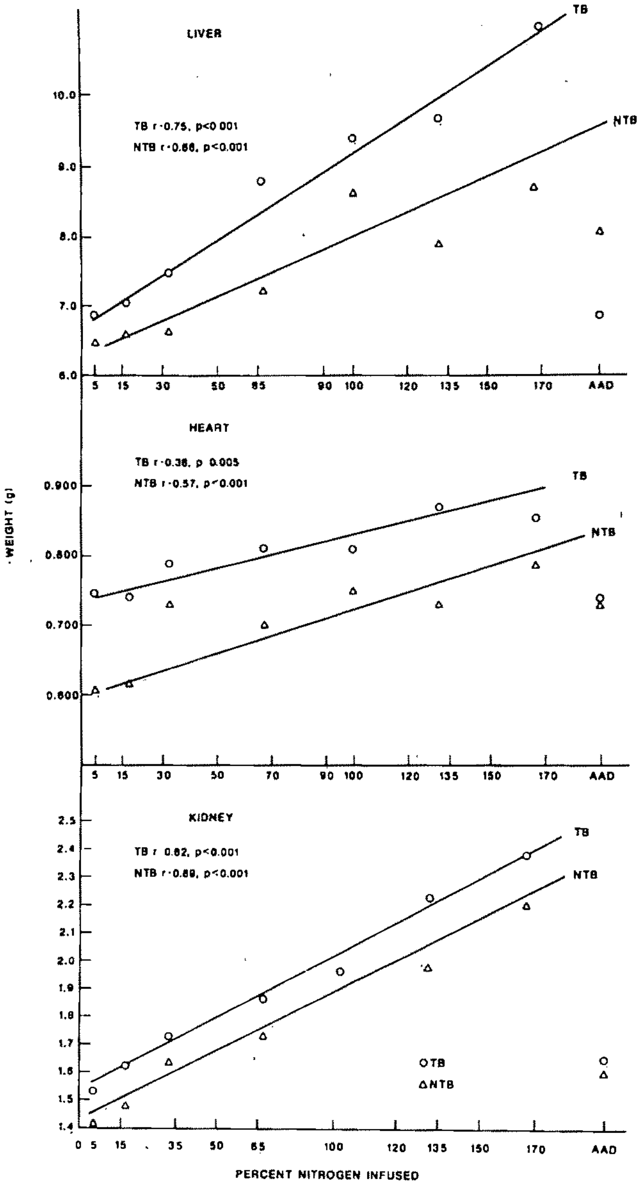

FIG. 1. Response of liver, heart, and kidney to TB and NTB status, to changes of nitrogen substrate infusion from 5–167% of normal, and to oral diet (AAD). Data points are mean values, and correlation coefficients are calculated with infusion data only.

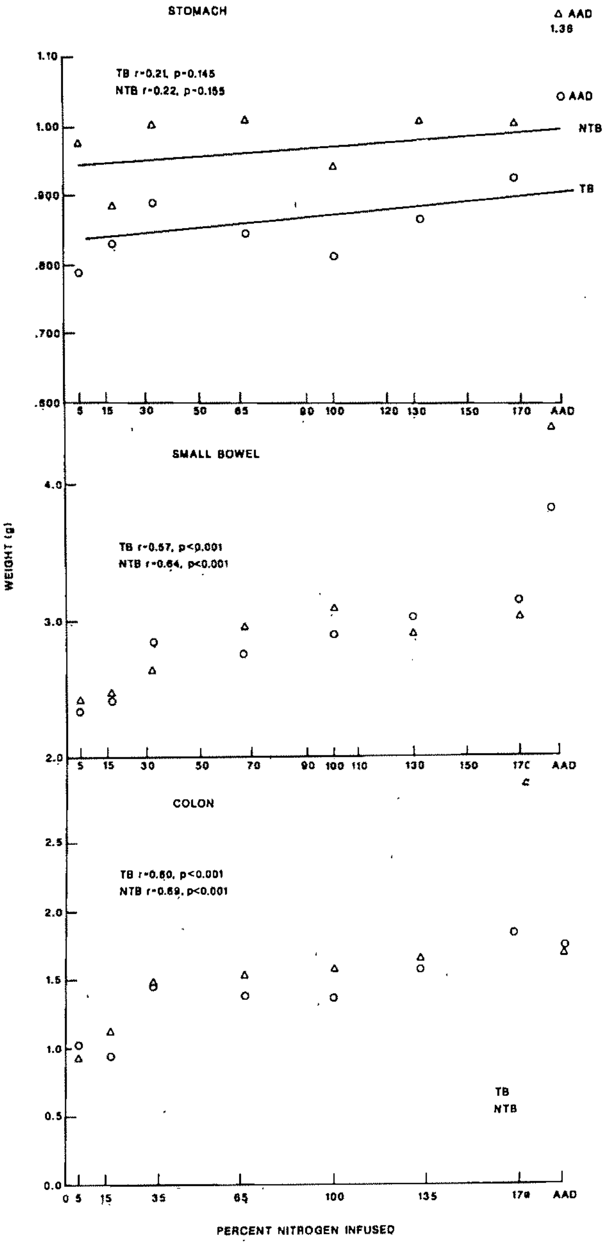

FIG. 2. Response of stomach, small bowel, and colon to TB and NTB status, to changes of nitrogen substrate infusion from 5–167% of normal, and to oral diet (AAD). Data points are mean values, and correlation coefficients are calculated with infusion data only.

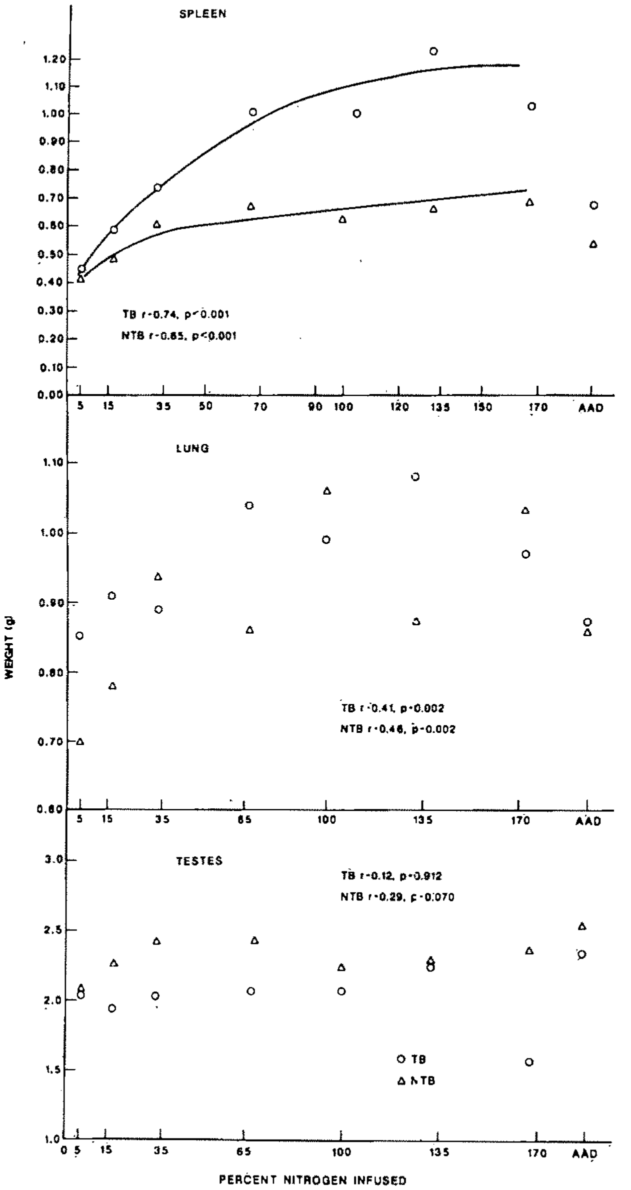

FIG. 3. Response of spleen, lung, and testes to TB and NTB status, to changes of nitrogen substrate infusion from 5–167% of normal, and to oral diet (AAD). Data points are mean values, and correlation coefficients are calculated with infusion data only.

body weights of NTB-AAD rats. The final carcass weights of TB-AAD rats were significantly less than the final carcass weights of NTB-AAD rats (p < 0.001).

Total carcass content of water tended to be lowest in the 5%, 16%, and 33% infusion groups of rats in both the TB (r = 0.30, p = 0.034) and NTB (r = 0.48, p = 0.001) groups (Fig. 5). Carcass protein content correlated significantly with infused nitrogen intake for NTB rats (r = 0.62, p < 0.001), but not for TB rats (r = 0.19, p = 0.179, Fig. 6). No significant differences were detected in the fat content (Fig. 7) or in percentage of water, TB protein, or fat content between any of the infused groups (Figs. 5–7). All of the infused groups had a higher total body fat content when compared to orally fed control animals (Fig. 7).

Tumor Growth and Composition

Tumor weight varied significantly with rate of nitrogen infusion (r = 0.35, p = 0.012). TB-005 animals had

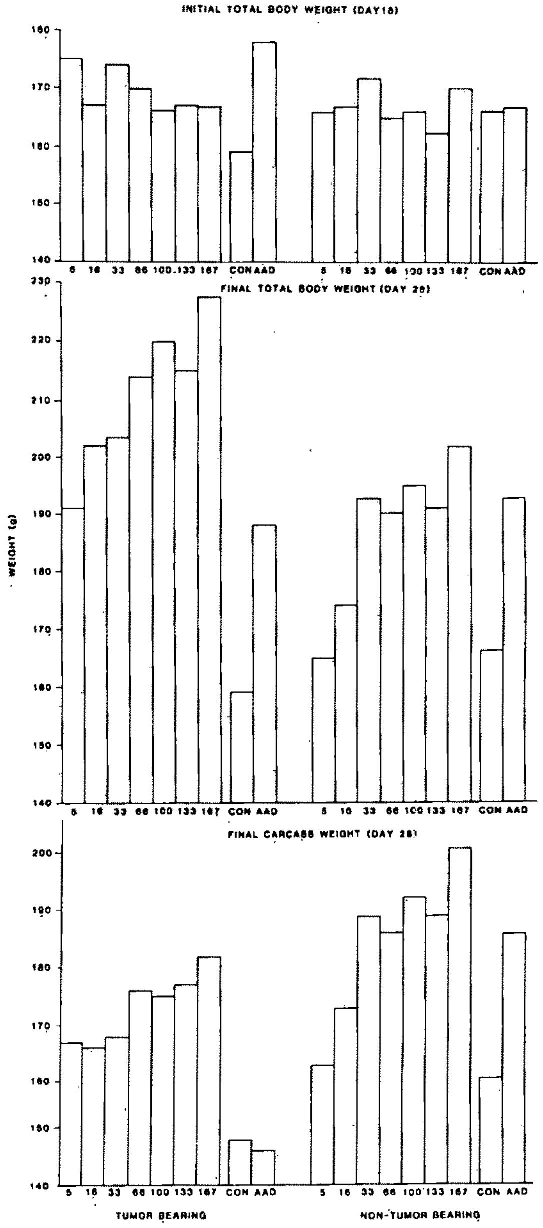

FIG. 4. Mean values of initial total body weight, final total body weight, and final carcass weight (carcass weight = total body weight − tumor weight − gastrointestinal tract content) for TB and NTB rats infused with TPN solution with nitrogen content varying from 5–167% of normal. Mean weights of a cohort of control rats killed on the initial day (day 18) of infusion (CON) and groups maintained on an oral diet (AAD) are also indicated. No significant differences were detected among mean initial total body weights. Final mean total body weights (TB: r = 0.55, p < 0.001; NTB: r = 0.70, p < 0.001) and carcass weights (TB: r = 0.40, p = 0.003; NTB: r = 0.69, p < 0.001) varied directly with rate of infused nitrogen.

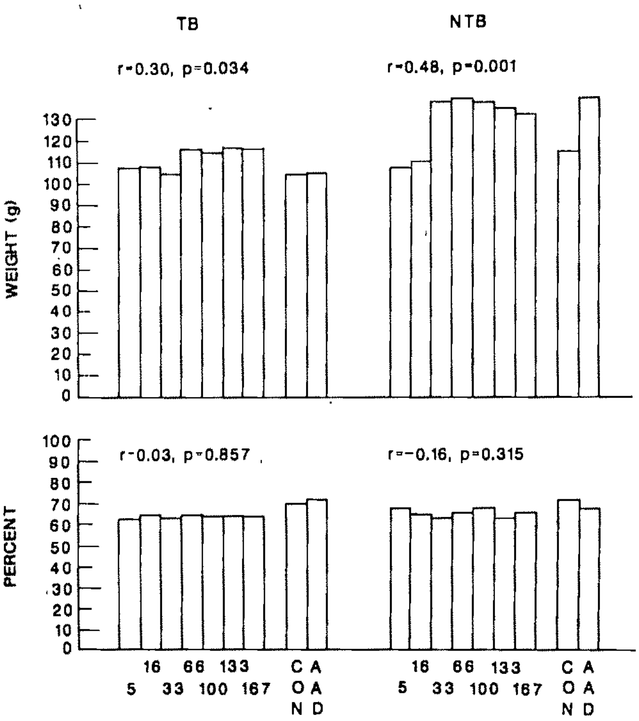

FIG. 5. Carcass water content expressed as absolute weight and as a percentage of carcass weight for rats receiving TPN infusions, control rats (CON), and orally fed rats (AAD). Each bar is a group mean value, and correlation coefficients are calculated with infusion data only.

the lowest tumor growth rates, whereas TB-167 had the highest (Fig. 8). Differences were less prominent at infusion rates between these extremes (Fig. 8, Table 2). The ratio of tumor weight to carcass weight (0.140) was lowest in the TB-005 animals and similar in the remainder of the infused TB rats (ratio range: 0.198 to 0.234, Table 2). The ratio was highest (0.272) in the TB-AAD group.

Tumor protein content was significantly related to the rate of nitrogen infusion ($r = 0.48$, $p < 0.001$, Table 2). No significant relationships were detected between tumor water or fat content and rate of nitrogen infusion (Table 2).

Discussion

These data indicate the effects on a host-tumor system of widely varying nitrogen intake associated with constant caloric, fat, mineral, and vitamin intakes. The survival data indicate that both the extremes, of either no nitrogen (0%) or high nitrogen (133% or 167%), are poorly tolerated by the TB host. No TB animals survived the 10-day experiment at 0%, and survival was difficult to obtain in the TB-133% and TB-167% groups (Table 1). When mechanical and infectious failures were eliminated, survival was easy to obtain in all of the other TB groups (5–100%) and in all of the NTB groups (5–167%).

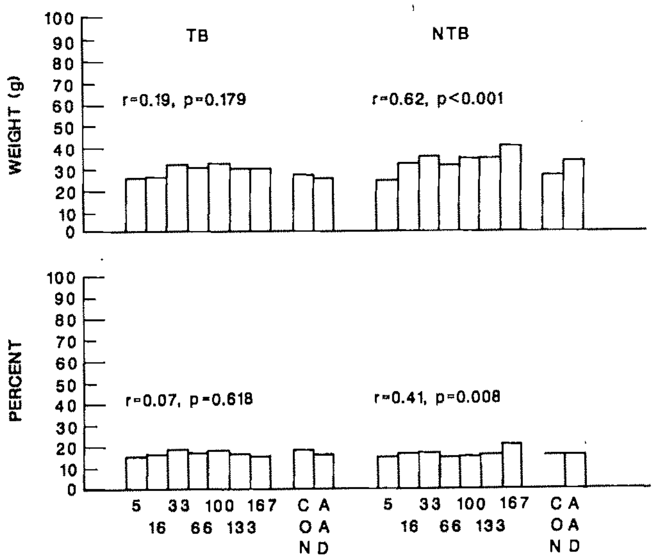

FIG. 6. Carcass protein content expressed as absolute weight and as a percentage of carcass weight for rats receiving TPN infusions, control rats (CON), and orally fed rats (AAD). Each bar is a group mean value, and correlation coefficients are calculated with infusion data only.

The blood studies, organ weight data, and carcass analysis data can be examined to determine possible pathophysiology and causes of death in the TB animals at both extremes of nitrogen intake. The anemia and polymorphonucleocyte response have been repeatedly observed in this model.[4,5] There were no correlations of hematocrit or white blood cell count with the rate of nitrogen infusion in this experiment, and there have been no correlations of tumor size with these parameters

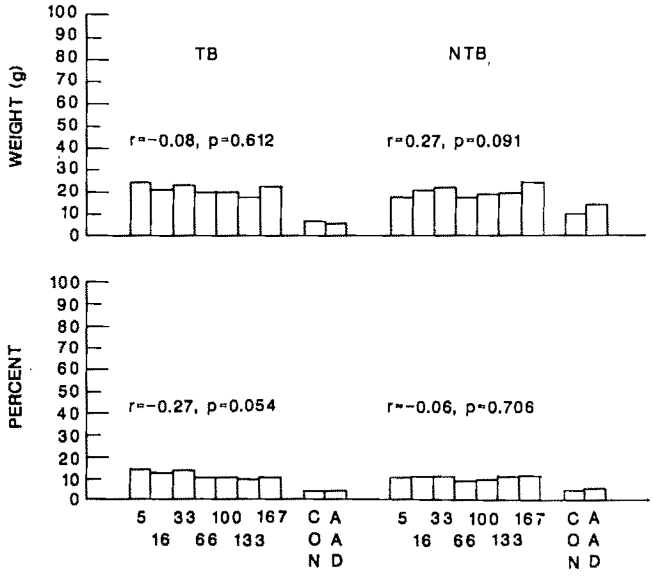

FIG. 7. Carcass fat content expressed as absolute weight and as a percentage of carcass weight for rats receiving TPN infusions, control rats (CON), and orally fed rats (AAD). Each bar is a group mean value, and correlation coefficients are calculated with infusion data only.

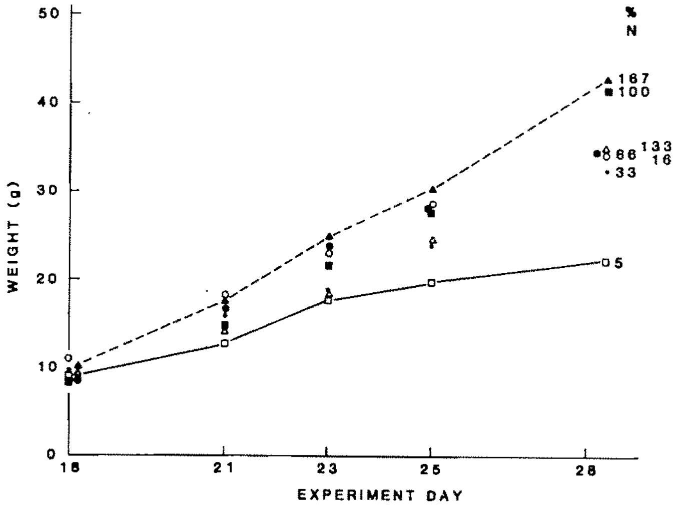

FIG. 8. Mean tumor weights calculated from *in vivo* measurements[6] (days 18 to 25) and final measured (day 28) mean tumor weights for rats receiving isocaloric TPN infusions with nitrogen content ranging from 5–167% of normal. Tumor growth lines are graphed only for the most rapidly growing T = 167% group and most slowly growing T = 5% group.

in either this experiment or other experiments.[4,5] The mechanism for the anemia is totally unknown. The elevated white blood cell and count shift in differential count can be hypothesized to be a reaction to areas of tumor necrosis. These data suggest that both the anemia and leukocytosis are nonspecific stresses in the TB host when significant tumor volume is reached. They are not present in the NTB host, and they probably are causes of increased mortality rates and poor tolerance of nutritional stresses in the TB host.

These organ weight data suggest several different patterns of pathophysiology. The liver, heart, and kidney weights all suggest a nonspecific detrimental effect of the tumor acting at all levels of nitrogen infusion and a clear relationship of weight to the rate of nitrogen infusion (Fig. 1). This nonspecific effect of the tumor, which causes increased liver, heart, and kidney weights, might be explained by the anemia and toxic factors causing the granulocyte response. The extra demands of anemia and toxicity require both increased cardiac output and increased glomerular filtration leading to hypertrophy of these organs. The liver also usually responds to nonspecific toxic stress with fat accumulation and increased weight. This phenomenon has been repeatedly observed in this model.[4,5] Alternative hypotheses such as tumor-produced growth factors causing organ hypertrophy cannot be excluded. The linear response of liver, heart, and kidney to the rate of nitrogenous substrate infusion would also be expected. Increased liver capacity would be required to process the increased amino acid load, and both increased kidney perfusion (cardiac output) and increased renal clearance of nitrogen as ammonia and urea would be required by the host to cope with the increasing levels of nitrogen substrate.

The reasons for the observed changes in stomach weights are unclear. Specific responses of stomach weights to the TB state in this model have not previously been observed. Similarly, one would not expect the stomach to be particularly responsive to rate of nitrogenous substrate infusion. The small bowel weights and stomach weights demonstrated a marked decrease in weight when TPN animals are compared to orally fed animals (Fig. 2). This has been repeatedly demonstrated in similar previous comparisons.[18,24] Small bowel, colon, spleen, and lung all demonstrated a tendency toward low weights in the 5% and 16% TB and NTB groups. These changes suggest simple nitrogenous substrate deprivation in rapid turnover tissues that should be substrate-sensitive. The absence of major differences between the TB and NTB groups suggests that the tumor is not particularly successful at competing for nitrogenous substrate with these tissues.

The pattern of spleen weights observed with the changes in nitrogen substrate is of interest. Elevated spleen weights are consistently observed during tumor growth in most of the transplantable rodent-tumor models.[5,7,15] The mechanism of this response is not well understood but probably involves the immunologic re-

TABLE 2. *Tumor Weight and Composition*

Nutritional Group	n	Initial Weight* (g)	Final Weight (g)	Day 18 TW/CW†	Water Content (%)	Fat Content (%)	Protein Content (%)
005	10	9.2 ± 1.6	23.4 ± 3.0	0.140	85.9 ± 1.4	2.2 ± 0.4	8.8 ± 0.9
016	9	10.9 ± 2.0	34.9 ± 5.4	0.209	86.2 ± 0.6	1.3 ± 0.1	8.6 ± 0.3
033	6	9.9 ± 1.6	33.3 ± 3.3	0.198	86.3 ± 0.7	1.6 ± 0.2	10.1 ± 0.7
066	11	9.7 ± 1.8	35.8 ± 4.3	0.203	86.5 ± 0.6	1.3 ± 0.2	10.0 ± 0.6
100	11	8.1 ± 1.0	42.3 ± 4.6	0.241	86.3 ± 0.8	1.2 ± 0.1	10.3 ± 0.8
133	2	9.4 ± 0.6	35.7 ± 13.8	0.201	82.5 ± 0.5	1.7 ± 0.6	12.8 ± 0.3
167	3	9.8 ± 1.4	42.6 ± 11.3	0.234	84.2 ± 0.3	1.3 ± 0.3	12.4 ± 0.3
CON	6	5.8 ± 2.3	—	—	84.9 ± 3.0	0.8	14.2 ± 1.9
AAD	6	14.4 ± 3.6	39.8 ± 9.5	0.272	85.1 ± 0.8	1.1 ± 0.4	11.9 ± 1.0

Values are given as mean ± SEM.
* Initial weight calculated from *in vivo* tumor dimensions.[6]
† Tumor weight to carcass weight ratio.
n = number of rats in group.

sponse to the tumor. Data from this experiment suggest that this mechanism is extremely nitrogen-substrate–responsive since the response almost totally disappears at low levels of nitrogen infusion (Fig. 3).

These total body weight data and carcass weight data (Fig. 4) indicate the influence of the TB state under both infused substrate and free-feeding substrate conditions. Total body weights for all of the infused animals are higher for the TB groups when compared to the NTB groups and are similar in the TB-AAD and NTB-AAD groups. Subtraction of the tumor weights to derive carcass weights (Fig. 4) shows the diminished carcass mass in the infused TB groups and markedly decreased carcass mass in the free-feeding TB-AAD group when compared to the respective NTB groups. These data are consistent with previous studies of this model, which all suggest that decreased carcass mass in the free-feeding animal is largely due to decreased substrate intake[4–6,19] and that the carcass mass in the TB state can be partially preserved with an infusion of adequate nutrients.[4–6] Of particular interest is the relatively similar carcass mass in the TB 5%, 16%, and 33% groups (Fig. 4). These data, along with the body composition data and data regarding the small bowel, colon, spleen, and lung weights all suggest that the tumor is not particularly successful in competing with normal carcass and visceral tissues for limited nitrogenous substrate.

Carcass composition data (Figs. 5–7) simply confirm that the overall carcasses were of similar composition. This is particularly evident when the carcass composition is expressed as a percentage of overall carcass weight. These data indicate that the preservation of carcass mass in the infused TB groups is the result of satisfactory accumulation of lean tissue rather than pathophysiologic accumulation of either fat or water. The tendency of infused groups to accumulate slightly more fat than orally fed groups (Fig. 7) has been observed in other comparisons of infused animals *versus* free-feeding animals[4,18] and remains consistent.

The tumor weight data (Fig. 8) and tumor composition data (Table 2) suggest that the tumor is responsive to the quantity of nitrogenous substrate available and that tumor growth is inhibited at the 5% level of nitrogenous substrate infusion. The finding of decreased tumor growth only at the 5% level with failure of animal survival at the 0% level indicates that a selective beneficial effect to the host-tumor system occurred only in a very narrow range of nitrogen infusions. The low tumor weight to carcass weight ratio (Table 2) and relatively normal carcass composition (Fig. 5–7) indicate a selective detrimental effect of low nitrogenous substrate availability on the tumor.

This finding of tumor inhibition with this balanced amino acid solution is of interest in light of recent determinations by our laboratory and other laboratories of the amino acid substrate requirements of this MCA tumor.[25,26] The work by Miller et al.[25] had demonstrated a major requirement of this tumor for the amino acids glutamine and asparagine. These amino acids have been demonstrated to be important for growth in other tumor systems.[27,29] These latter findings are particularly interesting in that 33% of the amino acid substrate used in the current experiment was composed of glutamine, asparagine, glutamic acid, and aspartic acid.[18] All of these data suggest that further beneficial manipulations in this host-tumor system might result from purely nutritional manipulation of the amino acid composition of the infused formula while keeping the total nitrogen levels in the 5% range.

The results of our study are not unique in demonstrating decreased tumor growth in response to nitrogen deprivation. Early research in the nutrition and cancer field clearly demonstrated that poor nutritional intake and, to a certain extent, protein depletion resulted in low rates of tumor formation, tumor transplantation rate, and tumor growth in rats and mice when compared to well-fed control animals.[30,31] One of the early concerns in the development of antineoplastic chemotherapy was that it might exert an antitumor effect from a starvation mechanism rather than a direct tumoricidal effect of the drug.[30] More recently, the effects of protein depletion on tumor and host have been investigated using a variety of tumor models and experimental designs. Decreased tumor growth as a response to chronic protein malnutrition has been clearly demonstrated in four of these studies.[32–35] In three other studies in which rate of tumor growth and host survival have been investigated, the combination of decreased tumor growth and prolonged host survival compared to normally nourished TB control animals has been demonstrated.[36–38] One problem with these studies is that none of them report total food intake in detail, and most have been done with unbalanced orally fed diets. Since rats and mice frequently do not eat unbalanced diets or incomplete diets, and since total substrate depletion can have a profound effect on tumor growth,[4–10,16,17,30,31] it is difficult to know whether the diminished tumor growth obtained was due to total substrate deprivation or to the selective effect of nitrogen deprivation. These data reported in this study are unique in that the total food intake has been tightly controlled and the nitrogen intake has been varied over a wide range. The findings of diminished tumor growth and reasonable carcass composition at the 5% level therefore suggests a very specific effect.

The long-term effect on the host with a malignant tumor of a prolonged treatment with a low nitrogen diet is difficult to predict from available information. The usual clinical sequela of protein deficiency is the syndrome known as kwashiorkor, which consists of severe edema, low serum albumin concentration, fatty liver, total body potasium and magnesium depletion, and decreased plasma branched-chain amino acid concentration.[39] This is very different from the syndrome that occurs with protein and calorie depletion in which the primary features are severe wasting of both subcutaneous fat and muscle, which is the pattern usually observed with advanced malignancy. During this experiment, little evidence of either kwashiorkor or the protein calorie (marasmus) pattern of malnutrition was observed in any of the surviving animals, including those TB 5% animals in which decreased tumor growth was evident. There is, however, the very definite possibility that the kwashiorkor-like syndrome or other forms of malnutrition would develop in either TB rats or cancer patients maintained on low nitrogen diets over long periods of time. Development of these problems will depend upon the levels of nitrogen and energy given, amino acid composition of the nitrogen given, and the efficiency with which the normal adaptation mechanisms to low nitrogen intake function.[40] While these factors have been studied with regard to the prevention and treatment of starvation[39,41] and the determination of adequate levels of nitrogen intake for positive nitrogen balance,[42-44] detailed studies of nitrogen deprivation in cancer-bearing patients have not been reported. The animal work previously cited, however, does suggest that a survival advantage might occur under low nitrogen situations.[36-38] It should be mentioned that it is widely assumed that the host-tumor can compete more successfully than the host-carcass for nutritional substrate. This is based primarily on studies of an animal tumor system of glucose kinetics.[45] It should be stressed that it is only an assumption with regard to protein metabolism and tumor amino acid uptake and that this concept has never been carefully studied.

These data may be summarized as indicating that selective starvation of the host tumor has been accomplished by a nutritional manipulation, which has also resulted in reasonable preservation of host carcass. If these findings can be corroborated and extended with other animal work, they suggest a possible therapeutic approach to some patient populations with advanced tumor conditions.

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Bronchobiliary Fistulas in Adults

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Reported herein are 16 cases of nontraumatic bronchobiliary fistula in adults observed over 32 years. The fistulas were due to either biliary obstruction or infectious diseases involving the liver. All patients had biloptysis and other respiratory symptoms, and most had cholangitis, jaundice, and/or sepsis. The diagnosis was established by fistulography or cholangiography. All patients except one were treated surgically by relief of biliary obstruction and drainage of intra-abdominal abscesses. All 15 surgically treated patients had a successful outcome. Rapid diagnosis and early treatment of septic complications are necessary, but careful assessment and surgical relief of the biliary obstruction are essential in successfully treating this condition.

BRONCHOBILIARY FISTULA is defined as the passage of bile in the bronchi and presence of bile in the sputum (biloptysis), the pathognomic sign of the lesion; bronchobiliary fistula usually occurs either in the congenital form or following thoracoabdominal trauma. However, it can also occur as a rare complication of diseases of the biliary tract. In this situation the fistula can be due either to obstruction of the bile ducts or to infectious diseases involving the liver (hydatid cysts, echinococcosis, or amebic abscess). Management of these fistulas is often very difficult and can be associated with high morbidity and mortality rates. Early recognition and proper management are essential to avoid a fatal outcome. In this report we outline our experience with 16 cases of acquired, nontraumatic bronchobiliary fistulas in adults.

Patients

Between 1954 and 1985, 16 cases of bronchobiliary fistula were referred to Hôpital Bichat (1954–1970, surgical service of Dr. Jacques Hepp) and Hôpital Paul Brousse, Paris, France. We have reviewed these patients with respect to clinical features, diagnosis, treatment, and results. Patients with pleurobiliary fistulas were excluded. There were eight women and eight men with a mean age of 41.4 years (range: 21–65 years).

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Etiology (Table 1)

Associated iatrogenic injury of the bile ducts was present in eight cases. A postoperative stenosis of the bile ducts was present in five patients following cholecystectomy and in another patient following hepaticojejunal anastomosis for biliary carcinoma. Two other stenoses developed following gastrectomy and duodenopancreatectomy. In eight patients the main etiologic factor was chronic hepatic infection, but all these patients had previously undergone surgical intervention. Biliary obstruction was present in six of these patients, and in one this was clearly shown to be due to iatrogenic injury of intrahepatic bile ducts and in the other, to associated sclerosing cholangitis following injection of iodine solution in the bile ducts. Biliary obstruction was not demonstrated in one patient requiring reoperation for a recurrent hydatic cyst nor in the patient presenting with an amebic abscess.

Clinical Features

Respiratory symptoms, jaundice, and cholangitis were the cardinal clinical features of bronchobiliary fistula in this series. All 16 patients had bile in the sputum (biloptysis) and 11 of these patients gave a longer history of chronic irritable cough productive of greenish sputum. Seven patients presented with acute fulminating

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TABLE 1. *Etiology of Bronchobiliary Fistula*

Postoperative stenosis	8
Biliary surgery	6
Gastric and pancreatic surgery	2
Hydatid cyst	6
Echinococcosis	1
Amebic abscess	1

TABLE 2. *Symptoms and Signs of Sixteen Instances of Bronchobiliary Fistulas*

Symptoms	No. of Patients
Biloptysis	16
Jaundice	14
Cholangitis	15
External biliary fistula	9
Subphrenic abscess	11

bronchopneumonitis and dyspnea. Jaundice was present in 14 patients and acute cholangitis occurred in 16 patients. Nine patients had an external biliary fistula. Finally, 11 patients had fever and right upper quadrant abdominal pain associated with subphrenic abscesses (Table 2).

Radiologic and Laboratory Investigations

Chest x-ray demonstrated a right lower lobe pneumonia in five cases (Fig. 1). However, it was often difficult to demonstrate the fistula itself before surgery. The most reliable way was to perform a fistulogram when an external fistula was present (nine cases) (Fig. 2). In two instances, percutaneous transhepatic cholangiography was useful (Figs. 3 and 4). An HIDA scan was performed in two instances and demonstrated the fistula in both cases. Bronchograms were done in three instances but demonstrated the fistula in only one case. In seven cases, after surgery T-tube cholangiography demonstrated the fistula (Table 3). Laboratory investigations always revealed leukocytosis, increased serum bilirubin levels, and sputum containing bilirubin and multiple microorganisms. In ten cases the same microorganisms were found in the bile.

Operative Findings

A total of 42 operations were performed on these 16 patients (range: 1–5 operations per patient) (Table 4). Of these operations, 14 were performed in other hospitals prior to admission to Bichat-Paul Brousse Hospitals. In our institution, treatment of the bronchobiliary fistulas necessitated 26 operations on the 16 patients (range: 1–3 operations per patient).

All of the fistulas were on the right side of the chest. In 11 cases, a subphrenic abscess was present. In one instance, a pleurobiliary fistula (due to percutaneous transhepatic cholangiography) was associated with the bronchobiliary fistula. Underlying diseases of the bile ducts and/or the liver have previously been described.

Treatment

Operation was carried out in all but one patient who was admitted to our institution at a late stage and in an extremely poor condition, which prevented any aggressive therapy prior to death. The primary goals of surgery were to treat biliary obstruction if this was present, and to drain all abscesses. Relief of biliary obstruction was required in all except two cases (one amebic abscess and one hydatid cyst). Biliary drainage procedures included Roux-en-Y hepaticojejunostomy (four patients), choledochoduodenostomy (one patient), T-tube stenting (six patients), and fistula anastomosis (two patients). Subphrenic abscesses were drained in 11 patients. Right lower pulmonary lobectomy was carried out in only one patient, although this procedure has been carried out in three patients before referral.

Outcome

No mortality rate was observed among the 15 patients who were operated on.

Case Reports

In order to emphasize the diagnostic and therapeutic problems encountered in patients with bronchobiliary fistulas, two illustrative case histories are presented.

Case 1

A 65-year-old female first presented in 1962 with attacks of right upper quadrant abdominal pain and was diagnosed as having cholelithiasis. No treatment was undertaken and she remained well until

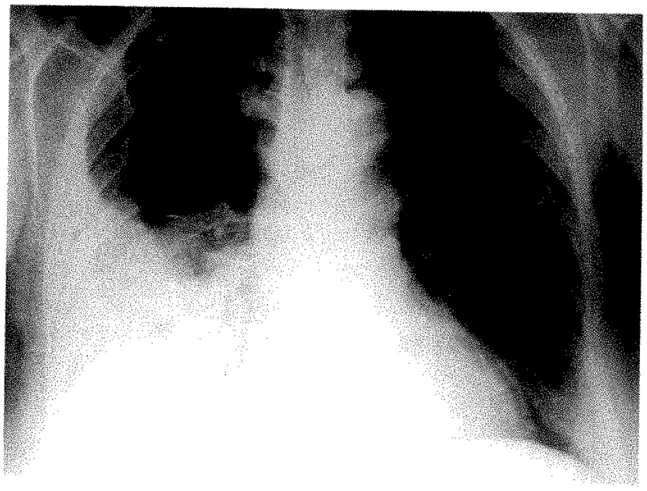

FIG. 1. Chest x-ray showing right lower lobe pneumonia.

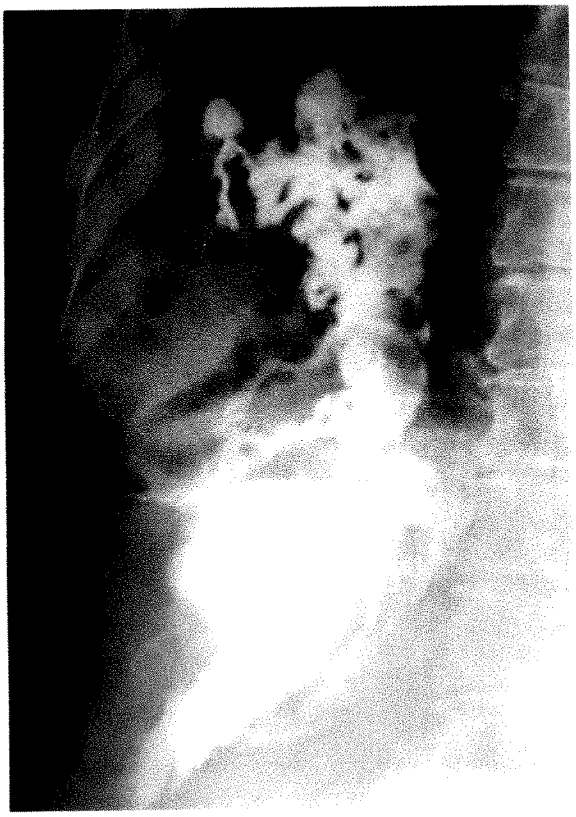

FIG. 2. Fistulogram showing large subphrenic abscess cavity communicating with the right bronchial tree. This patient had a postoperative stenosis of the bile duct following hepaticojejunal anastomosis for biliary carcinoma.

1972 when she began to have attacks of cholangitis. At that time cholecystectomy was undertaken and during surgery a sclerotic narrowing was found at the junction of the cystic duct and the hepatic duct. This area was excised and a hepaticoduodenostomy was performed. Nine months later she began to have further attacks of cholangitis with persistent cholestatic jaundice. A percutaneous liver biopsy in the posterior axillary line was performed and showed marked cholestasis with leucocytic infiltration but no evidence of fibrosis or cirrhosis. The biopsy was followed by a bile-stained pleural effusion and biloptysis. The pleural effusion was drained, which resulted in an external biliary fistula and biliopurulent discharge. She was then referred to this hospital with three problems: (1) recurrent cholangitis; (2) bronchobiliary fistula; and (3) external biliary fistula.

On admission she was jaundiced and in poor general condition, weighing 55 kg. She had hepatomegaly but no signs of hepatic insufficiency or portal hypertension. The white cell count was 23,000 and the liver function tests showed a cholestatic picture. A fistulogram showed a large abscess cavity, which was probably below the diaphragm. A percutaneous transhepatic cholangiogram displayed markedly dilated intrahepatic bile ducts with an obstruction just below the hilar confluence. Surgical exploration of the cavity was performed and three drains were inserted. At the same time an external biliary drain was inserted. After operation the abscess cavity regressed satisfactorily, but the bile drainage was irregular and unreliable despite several changes of drain. After 3 weeks the bile drainage stopped completely, and this was followed by septicemia and rigors. Surgical exploration was undertaken. A tumor of the common bile duct was found at the previous hepaticoduodenal anastomosis, and it was causing complete obstruction of the biliary tree. There were several stones above the stenosis. The tumor was completely excised and a hepaticojejunal anastomosis was performed, going up high on the left hepatic duct, and using a long Roux-en-Y loop. After operation the jaundice regressed satisfactorily and she was discharged with no further biliary problems. The histology confirmed a well-differentiated adenocarcinoma with widespread invasion of the submucosa and muscularis mucosae of the duodenum.

Case 2

A 43-year-old female was referred in 1984 for treatment of an external biliary fistula. In 1977, she had epigastric pains and hepatomegaly, and a surgical hepatic biopsy revealed steatosis. A second operation was undertaken 6 months later for a right subphrenic abscess. She was in good condition after surgery until January 1983 when she developed biloptysis. In March 1983 a thoracotomy was performed along with a pleural decortication, right middle pulmonary lobectomy, and suture of the bronchus. There was a 1.5 cm hole in the diaphragm that was also oversewn. External percutaneous hepatic biliary drainage was instituted during this operation. After surgery, the drain continued to yield bile, and the patient was referred to this hospital.

On admission on January 1984, she was in a poor general state and weighed 50 kg for 1.65 m. She was not jaundiced and had no signs of hepatic insufficiency or portal hypertension. She had a low grade pyrexia and a leucocytosis. Ultrasound examination of the liver showed a normal sized liver with aerobilia and no dilatation of the intrahepatic bile ducts. Fistulography showed opacification of the right biliary tree with narrowing of the right biliary duct and without opacification of the common bile duct. Percutaneous hepatic cholangiography showed dilatation of the left biliary branches. An ERCP was then performed; it revealed complete obstruction of the hilar confluence. Arteriography showed thrombosis of the right branch of the hepatic artery. A surgical

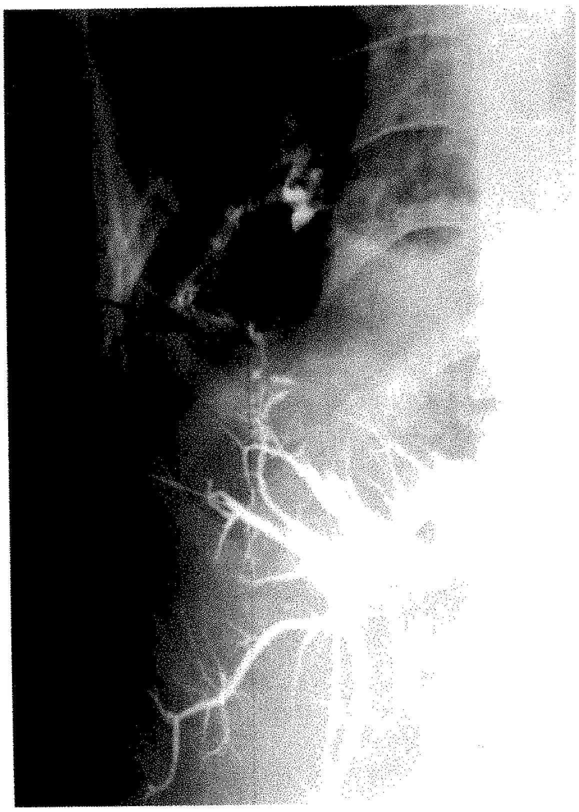

FIG. 3. Percutaneous transhepatic cholangiography (anteroposterior view) showing normal intrahepatic bile ducts and a fistulous communication (arrow) with the right bronchial tree. This bronchobiliary fistula was secondary to surgical excision of hydatid cysts.

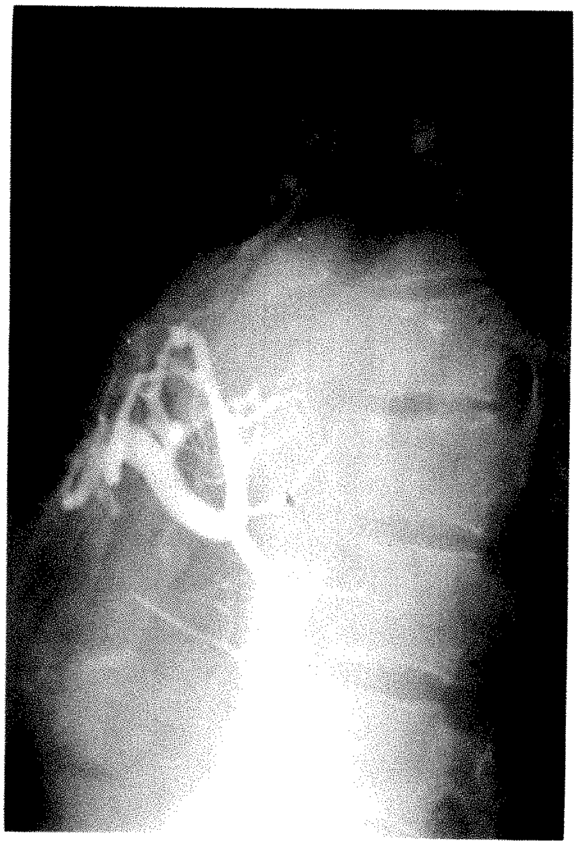

FIG. 4. Percutaneous transhepatic cholangiography (lateral view) from the same patient.

exploration was undertaken. The right lobe was hypertrophied, and there was left lobe atrophy. A stenosis of the primary bile duct confluence extending to the right secondary confluence was found, and there were several stones above the stenosis. An external biliary fistula and a biliodudenal fistula were also present. After dissection of the hilus, opening of the right and left biliary branches, and removal of the stones, a direct mucosa to mucosa anastomosis was performed between a Roux-en-Y loop of jejunum and the right primary hepatic branches. The left main hepatic duct was also included in the anastomosis. Two silastic biliary stent drains were placed across the anastomoses in the two right hepatic branches and exteriorized percutaneously via the Roux-en-Y loop.

Histologic examination showed fibrosis without any sign of neoplasia.

The postoperative course was uneventful, and she was discharged on the 16th postoperative day. On follow-up, she has remained well and has improved her state of nutrition. The drains were removed 18 months later and she has remained asymptomatic.

Discussion

Bronchobiliary fistulas are extremely rare, and we have not encountered the congenital forms[1,2] or bronchobiliary fistulas secondary to thoracoabdominal trauma[3,4]. The first description of a bronchobiliary fistula was that of Peacock in 1850 in a patient with a hydatid cyst.[5] In 1938, Ochsner described a 4% incidence of bronchobiliary fistulas in 453 pyogenic liver abscesses[6] and a 10.5% incidence of bronchobiliary fistulas in 3608 subphrenic abscesses.[7] According to Morton and Phillips,[8] the second leading cause of bronchobiliary fistulas other than hydatid, echinococcal, or amebic abscess of the liver is obstruction of the common bile duct. Thus, two major factors are responsible for the formation of bronchobiliary fistulas: mechanical (bile duct obstruction) and infectious (subphrenic or intrahepatic abscess). In the present study, iatrogenic stenosis was present in half the cases, although all but two of the remaining patients with hepatic infection had an associated obstruction of the bile duct. The nature of this obstruction was not always easy to define and in most cases probably resulted from the presence of severe inflammation close to the primary lesion or in the hilus of the liver. The obstruction of the bile duct is usually due to lithiasis,[9,10] hydatid cyst,[10-14] or postoperative stricture.[15-17] Less common reported causes are carcinoma of the head of the pancreas,[16] ascaris worm in the bile duct,[8] or tuberculosis.[18] Bile duct obstruction leads to cholangitis, intrahepatic abscess, and rupture of this abscess into the pleural space or, if adhesions exist, into the bronchi. This explains the preferential location of bronchobiliary fistulas in the right side of the chest. However, some exceptional cases of bronchobiliary fistulas located in the left side have been described.[19,20]

The diagnosis is usually made clinically by the presence of bile in the sputum. This biloptysis may occur either as an acute pneumonitis or as a chronic irritable cough productive of greenish sputum. In patients with a long history of biliary tract disease, diagnosis is usually easy. However, in some cases signs are minimal, for

TABLE 3. *Radiologic Demonstration of Bronchobiliary Fistula in Sixteen Patients*

Percutaneous transhepatic cholangiography	2
T-tube cholangiography	7
Fistulography	9
Bronchography	3
Hida scan	2

TABLE 4. *Forty-two Operations Performed in Sixteen Patients with Bronchobiliary Fistula*

Bilioenteric anastomosis	
Hepaticojejunostomy	6
Choledochoduodenostomy	2
Cholecystojejunostomy	1
Fistulojejunostomy	2
T- tube stenting	6
Resection of hydatid cyst	6
Closure of the fistula	3
Subphrenic abscess drainage	10
Pleural drainage	2
Pulmonary resection	4

example, cough with yellow sputum.[21] Sutherland et al.[22] have described false bile ptyalism in patients with sickle cell disease and hemolytic crisis. However, if this condition can be excluded, the presence of bile in the sputum is pathognomonic of bronchobiliary fistula.

Bronchoscopy and bronchography rarely demonstrate the fistula and are not essential for either diagnosis or therapy. If an external fistula exists, a fistulogram is the best way to visualize the fistula. In its absence, transhepatic cholangiography[18] or endoscopic retrograde cholangiography[23] may be used. Cholescintigraphy using^{131}I rose bengal has permitted peroperative diagnosis of thoracobiliary fistula,[24] but Hida or pipida cholescintigraphy with delayed views are probably more reliable in detecting small bronchobiliary fistulas.[25-27]

Prevention of these fistulas by early diagnosis and treatment of the underlying cause is extremely important since treatment of established bronchobiliary fistula is usually very difficult. These patients frequently have had several previous operations, and they are usually severely ill with sepsis, malnutrition, and respiratory problems. In the chronic form, it is often necessary to prepare the patient for operation by antibiotic therapy, hyperalimentation, and respiratory physiotherapy. However, in the acute fulminating form, an agressive and rapid approach is necessary. A two-stage approach can be used: (1) external biliary drainage by percutaneous or surgical drainage of subphrenic abscess and/or direct percutaneous drainage of the intrahepatic biliary tract; and (2) treatment of the underlying cause. In patients with biliary obstruction, the priority is treatment of the biliary disease. This is best achieved by a transabdominal approach[15,16] in order to relieve bile duct obstruction and to obtain adequate drainage of all abscesses. In all cases, peroperative cholangiography must be performed. In the case of postoperative strictures, a bilioenteric anastomosis should be carried out. We consider Roux-en-Y hepaticojejunostomy to be the best technique, although this may be difficult when the bile ducts are small, as is usually the case with this condition. In cases due to stones, removal of all stones and bilioenteric anastomosis must be performed.[9] The transthoracic approach should be reserved for those rare patients who have irreversible pulmonary and bronchial damage, or for patients with a traumatic bronchobiliary fistula without biliary obstruction. In this situation a primary transthoracic approach allows pleural decortication and repair of the diaphragmatic disruption.[28]

In conclusion, nontraumatic bronchobiliary fistula in adults is a rare condition complicating bile duct obstruction and/or liver abscesses. Rapid diagnosis and early treatment of septic complications are necessary, but surgical relief of the biliary obstruction following full and careful assessment is essential.

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Minor Role of Ketone Bodies in Energy Metabolism by Skeletal Muscle Tissue During the Postoperative Course

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To evaluate changes of peripheral ketone body (KB) metabolism after operation, muscle metabolism in postsurgical patients was studied at 3 hours (S_I) and 24 hours (S_{II}) after surgery by the forearm catheter technique. Data were compared to those of equivalent fasted controls (C_I, C_{II}). In a manner consistent with enhanced mobilization of endogenous substrate stores, arterial concentrations of free fatty acids (FFA), 3-hydroxybutyrate (3-HOB), and acetoacetate (AcAc) were markedly elevated immediately after surgery. This increase was accompanied by a rise in muscular utilization of AcAc (S_I: 0.21 ± 0.05 μmol/100 g/min; C_I: 0.08 ± 0.05, $p < 0.05$) and 3-HOB (S_I: 0.24 ± 0.06 μmol/100 g/min; C_I: 0.11 ± 0.01, $p < 0.05$). Surprisingly, on the first postoperative day, concentrations of AcAc and 3-HOB fell below those of fasting controls. Concomitantly, the utilization rate of AcAc by muscle (S_{II}: 0.07 ± 0.03 μmol/100 g/min; C_{II}: 0.27 ± 0.04, $p < 0.05$) was significantly lower in patients than in controls. Reduction of the fractional extraction rate of AcAc (S_I: 38.4 ± 3.8%; S_{II}: 24.0 ± 6.1%, $p < 0.05$), as well as a net production of 3-HOB by muscle (S_{II}: −0.08 ± 0.05 μmol/100 g/min; C_{II}: 0.49 ± 0.13, $p < 0.05$) 24 hours after surgery indicated a reduced peripheral capacity for KB removal. Since this finding was related to a significantly higher rate of muscular glycerol production (S_{II}: −0.13 ± 0.03 μmol/100 g/min; C_{II}: −0.06 ± 0.02, $p < 0.05$), one may suggest that increased intramuscular availability of FFA from triglyceride hydrolysis was responsible for the impairment of peripheral KB utilization. These results indicate that KBs contribute little to energy metabolism in skeletal muscle tissue in the late postoperative phase.

KETONE BODIES (KBs) are important in mammalian metabolism, not only because of their role as substrates for energy metabolism, but also because of their regulatory function in the metabolism of several tissues. Thus, during periods of food deprivation, concentrations of KBs in blood (consisting mainly of 3-hydroxybutyrate [3-HOB] and acetoacetate [AcAc]) are significantly elevated above postabsorptive levels. Since ketones can serve as alternative energy-yielding substrates in brain, heart, kidney, and skeletal muscle, they reduce whole body glucose demand. Thus, gluconeogenesis and total body glucose turnover are attenuated.[1] Therefore, it was proposed that ketosis represents an important mechanism for conservation of body protein, since glucose production during fasting is primarily derived via gluconeogenesis from amino acids.[2]

In contrast to what is known about the fasting state, the physiologic role of KBs during postsurgical stress is only poorly understood. Following trauma or injury, an increased mobilization of endogenous fat stores occurs. This is known in healthy subjects to be followed by an increase in hepatic ketogenesis.[3] However, with the stress of surgery,[4] trauma,[5–7] or infection[5,8,9] the plasma concentrations of 3-HOB and AcAc remain low, even during caloric deprivation. Several investigators[10,11] have suggested that the lack of a ketotic response in surgical patients contributes to fuel deficiency in muscles and possibly to widespread protein catabolism. However, because of recent results[12,13] the possibility that KBs per se can preserve the amino acid pool, is questionable.

In addition, there are conflicting observations concerning the peripheral capacity for utilization of ketones following trauma or surgery. Whereas some authors re-

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TABLE 1. *Laboratory Data From Controls (N = 15) and Postsurgical Patients (N = 31)*

	Controls	Patients
Age (yr)	28.3 ± 2.4	34.7 ± 3.1
Height (cm)	177.7 ± 0.8	173.2 ± 2.1
Weight (kg)	75.2 ± 1.0	72.4 ± 1.5
Hb (g/dL)	14.4 ± 0.5	13.8 ± 0.4
SGOT (U/L)	10.5 ± 0.3	13.5 ± 3.2
Cholinesterase (U/L)	5693 ± 130	5235 ± 327
Prothrombin time (% of control)	94.1 ± 1.0	95.5 ± 5.2

Values are given as mean ± SEM.
Hb = hemoglobin. SGOT = serum aspartate-aminotransferase.

ported impaired removal of KBs,[8,14] others found a normal peripheral utilization of ketones according to their arterial supply.[5,15,16]

In the present study, the interrelationship between ketosis and peripheral KB utilization was investigated in the early and late postoperative periods, thus giving information on the dynamics of KB metabolism after surgery. Data were compared to those from fasting controls. By means of the forearm technique,[17] substrate metabolism of peripheral muscle tissue could be quantitated selectively.

Materials and Methods

Subjects

Two groups of normal subjects (C_I and C_{II}) and two groups of postsurgical patients (S_I and S_{II}) participated in the present study. Control subjects and patients were studied at different time points during a 36-hour fasting period, which was interrupted in patients by the surgical procedure. Detailed information on groups C and S is given in Table 1. Groups C_I and C_{II} consisted of ten (C_I) and five male (C_{II}) volunteers, recruited from medical students and the staff of the Munich University School of Medicine. None had a family history of diabetes mellitus, and a physical examination and laboratory tests excluded other diseases. All of the subjects consumed a weight-maintaining diet. Groups S_I and S_{II} consisted of 23 (S_I) and eight male (S_{II}) postsurgical patients, who were well matched by age and weight with the controls. All had undergone elective upper abdominal surgery for nonmalignant gallbladder and stomach diseases, and were within ±10% of ideal body weight before surgery. They had been in excellent health prior to surgery and did not exhibit glucose intolerance or hyperlipemia. None of the subjects received drugs known to alter glucose, insulin, or lipid metabolism. In all patients the postoperative course was uneventful. The nature, purpose, and possible risks involved in the study were carefully explained to all subjects and patients before seeking their voluntary signed consent.

Experimental Protocol

Protocols were reviewed and approved by the ethics committee of the German Research Council, corresponding to the Helsinki Declaration of 1975. Group C_I was studied after a 15-hour fasting period and group C_{II} after a 36-hour fasting period. During fasting, daily intake consisted only of at least 1500 mL of water; postsurgical subjects were fasted preoperatively for 10 hours. Metabolic measurements were performed in group S_I at 3 hours and in group S_{II} at 24 hours after surgery, thus corresponding in the duration of fasting to controls (C_I and C_{II}), if a mean duration of the surgical procedure of 2 hours is assumed. All patients received only saline infusion until metabolic measurements were completed.

Forearm Technique

As described originally by ANDRESS,[17] the forearm catheter technique represents an adequate method for investigation of metabolism in peripheral muscle tissue. The technique requires the simultaneous sampling of arterial and deep venous blood, together with the measurement of forearm blood flow. Thus, by means of a small teflon catheter (Vygon No. 11512, Vygon, Aachen, West Germany), a deep muscle vein of the forearm was cannulated in a retrograde manner. The patency was maintained by infusion of physiologic saline. A plastic cannula (Abbocath #18 gauge, Abbott, North Chicago, IL) was inserted into the radial artery and also perfused with saline solution. For metabolic measurements, arterial and deep venous blood samples were collected every 10 minutes throughout a 40-minute steady-state period. Forearm blood flow was measured by venous occlusion plethysmography. Flow determinations were taken after each blood sampling.

Analytical Procedures

Plasma insulin, glucagon, epinephrine, norepinephrine, glucose, lactate, pyruvate, free fatty acids (FFAs), 3-HOB, AcAc, glycerol, and blood oxygen concentration were measured as described previously.[9,18]

Calculations

Substrate concentrations of the four measurements at each time point were averaged to calculate substrate balances across muscle tissue. Substrate turnover by muscle was determined by multiplying the average forearm blood flow with arterio-deep venous concentration differences. Mean forearm blood flow was derived from several determinations at each time point. In order to quantitate the interrelationship between arterial substrate supply and substrate utilization by muscle, the extraction ratio (%E) was calculated by dividing the arterio-venous substrate concentration difference by the arterial substrate concentration.

Statistical Analysis

Data are expressed as the mean ± SEM. Statistical differences were tested by means of analysis of variance. A difference was considered significant if $p < 0.05$.

Results

In the immediate postoperative period, forearm blood flow corresponded to that of controls (C_I: 3.1 ± 0.1 mL/100 g/min; S_I: 2.9 ± 0.1). Twenty-four hours after surgery, however, forearm blood flow was significantly increased (C_{II}: 3.0 ± 0.1 mL/100 g/min; S_{II}: 4.5 ± 0.2 mL/100 g/min, $p < 0.05$).

As a sign of stimulated neuroendocrine response, arterial concentrations of glucagon, epinephrine, and norepinephrine were clearly elevated due to postoperative stress. In the first 24 hours epinephrine showed a moderate decline, whereas the concentration of glucagon rose significantly (Table 2). The increase in plasma insulin concentration after surgery indicated pancreatic B-cell stimulation by stress-induced hyperglycemia (Table 3).

Following surgery, the arterial concentrations of FFAs and glycerol rose significantly in comparison to those in fasting controls, reflecting accelerated mobilization of endogenous fat stores (Table 3). Subsequently, an increment of 3-HOB and AcAc concentrations over the normal fasting range could be observed. However, 24 hours after surgery arterial KB concentrations decreased to significantly lower levels when compared to those in corresponding controls.

In the postsurgical patients the plasma KB/FFA ratio also was significantly elevated 3 hours after surgery (S_I: 0.60 ± 0.08; C_I: 0.35 ± 0.06, $p < 0.05$) and decreased to 0.38 ± 0.07 (S_{II}) on the first postoperative day (significantly less then control value C_{II}: 1.91 ± 0.14, $p < 0.05$).

When compared to controls, utilization of AcAc by muscle rose significantly in the early postoperative period (C_I: 0.08 ± 0.01 μmol/100 g/min; S_I: 0.21 ± 0.05, $p < 0.05$; Fig. 1). This seemed to be due to an increased arterial supply of AcAc, since %E was similar in both groups (Table 4). Whereas net uptake of 3-HOB by muscle was simultaneously increased (C_I: 0.11 ± 0.01 μmol/100 g/min; S_I: 0.24 ± 0.06, $p < 0.05$), utilization of 3-HOB already appeared to be impaired at this time, as indicated by the reduced %E.

Twenty-four hours after surgery AcAc turnover by muscle was clearly reduced, compared to S_I (S_{II}: 0.07 ± 0.03 μmol/100 g/min, $p < 0.05$) and to corresponding controls (C_{II}: 0.27 ± 0.04 μmol/100 g/min, $p < 0.05$). In controls utilization of AcAc by muscle increased according to its arterial supply (%E remained unchanged); the decrease in AcAc utilization in the postsurgical subjects was more pronounced than could be expected from the reduced arterial supply since a simultaneous decrease of %E was observed. In addition, 24 hours after surgery a net production of 3-HOB by muscle occurred (S_{II}: −0.08 ± 0.05 μmol/100 g/min; Fig. 1) indicating greatly reduced utilization of KBs by muscle tissue at this time point ($p < 0.05$ *vs.* C_{II}: 0.49 ± 0.13 μmol/100 g/min). However, the uptake of 3-HOB in C_{II}, although higher than in C_I, occurred at a lower extraction ratio than in C_I, which points to a beginning impairment of peripheral KB removal also in the controls at this time point.

TABLE 2. *Arterial Concentrations of Insulin, Glucagon, Epinephrine, and Norepinephrine After a 15-Hour (I) and a 36-Hour Fasting Period (II) in Controls (C; I/N = 10; II/N = 5) and in Postsurgical Subjects (S; I/N = 23, II/N = 8)*

		C	S
Insulin (μU/mL)	I	7.1 ± 0.5	23.1 ± 3.4†
	II	4.3 ± 0.7*	15.3 ± 2.3*†
Glucagon (pg/mL)	I	99 ± 15	140 ± 21†
	II	128 ± 14*	277 ± 56*†
Epinephrine (pg/mL)	I	49 ± 7	188 ± 22†
	II	58 ± 8	112 ± 13*†
Norepinephrine (pg/mL)	I	242 ± 20	465 ± 68†
	II	231 ± 18	458 ± 48†

In patients fasted preoperatively for 10 hours, measurement I was done at 3 hours, measurement II at 24 hours after surgery.
Values represent mean ± SEM.
* Significant difference I *versus* II at $p < 0.05$.
† Significant difference S *versus* C at $p < 0.05$.

Arterial and muscle venous 3-HOB/AcAc ratio did not change during fasting in the two control groups (C_I

TABLE 3. *Arterial Concentrations of Substrates (mmol/L) and Oxygen (Vol%) After a 15-Hour (I) and a 36-Hour Fasting Period (II) in Controls (C; I/N = 10; II/N = 5) and in Postsurgical Subjects (S; I/N = 23; II/N = 8)*

		C	S
FFA	I	0.66 ± 0.03	1.14 ± 0.09†
	II	0.74 ± 0.04*	0.95 ± 0.07†
Glycerol	I	0.09 ± 0.004	0.15 ± 0.01†
	II	0.08 ± 0.02	0.16 ± 0.02†
AcAc	I	0.08 ± 0.01	0.19 ± 0.02†
	II	0.36 ± 0.03*	0.10 ± 0.01*†
3-HOB	I	0.15 ± 0.01	0.49 ± 0.07†
	II	1.05 ± 0.25*	0.26 ± 0.04*†
Glucose	I	4.71 ± 0.05	6.36 ± 0.19†
	II	4.08 ± 0.09*	5.56 ± 0.20*†
Lactate	I	0.41 ± 0.01	0.65 ± 0.07†
	II	0.46 ± 0.02	0.45 ± 0.06*
Oxygen	I	17.1 ± 0.2	16.9 ± 0.4
	II	17.0 ± 0.2	16.3 ± 0.4

Values represent mean ± SEM.
* Significant difference I *versus* II at $p < 0.05$.
† Significant difference S *versus* C at $p < 0.05$.

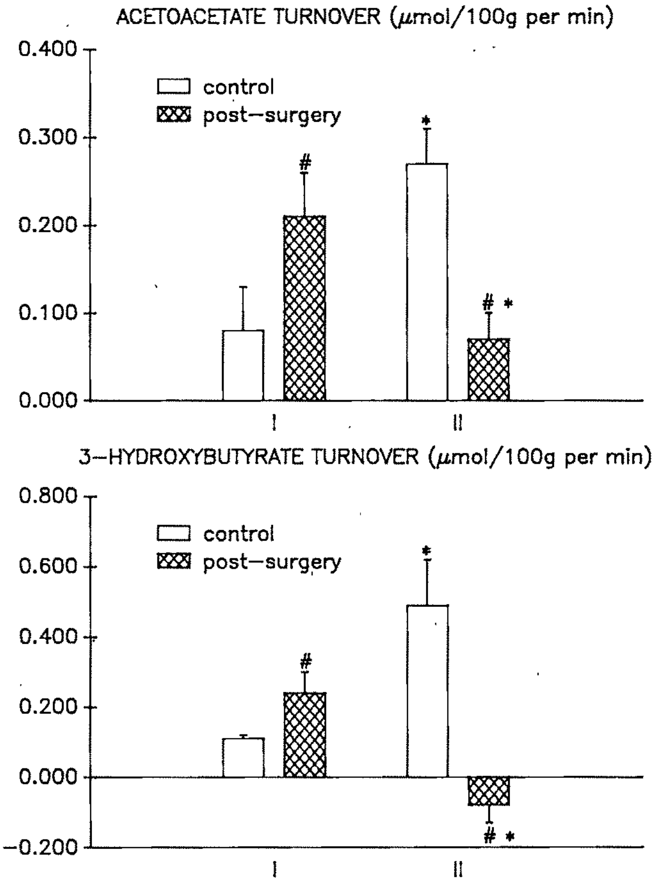

FIG. 1. Turnover rates of AcAc and 3-HOB by muscle after a 15-hour (I) and a 36-hour fasting period (II) in controls (I/N = 10; II/N = 5) and in postsurgical subjects (I/N = 23; II/N = 8). *p < 0.05 *versus* I. #p < 0.05 *versus* controls. All values represent the mean ± SEM.

and C_{II}). On the other hand, muscle venous 3-HOB/AcAc ratio was significantly higher in S_I and S_{II}, being consistent with a more reduced mitochondrial state of skeletal muscle during the postoperative period.

At each time point a significant correlation between arterial concentration of AcAc and its arteriovenous concentration difference was found in controls, which indicated the predominant role of the arterial supply of AcAc for its muscular uptake (Fig. 2). Postoperatively, however, a similar correlation could only be observed 3 hours after surgery, whereas 24 hours after surgery this correlation could no longer be demonstrated, suggesting a change in intracellular AcAc utilization.

Concomitantly, muscular glycerol release became elevated in the postoperative period (S_I: −0.08 ± 0.02 µmol/100 g/min; S_{II}: −0.13 ± 0.03, $p < 0.05$), suggesting simultaneously increased intramuscular lipolysis (Fig. 3). Additionally, at each time point, glycerol release exceeded the control values from fasted subjects significantly (C_I: −0.05 ± 0.004 µmol/100 g/min; C_{II}: −0.06 ± 0.02).

Immediately after surgery glucose uptake by muscle was elevated (S_I: 1.18 ± 0.17 µmol/100 g/min; C_I: 0.90 ± 0.04, $p < 0.05$), which was presumably due to the increased arterial supply, since %E of glucose was comparable (S_I: 6.5 ± 0.5; C_I: 6.4 ± 0.1). However, we observed a simultaneous increase in peripheral lactate production (S_I: −1.03 ± 0.40 µmol/100 g/min; C_I: −0.39 ± 0.02, $p < 0.05$). Twenty-four hours after surgery glucose uptake by muscle declined again, amounting at this time to 0.57 ± 0.25 µmol/100 g/min (S_{II}), which was comparable to that in fasted controls (C_{II}: 0.76 ± 0.06 µmol/100 g/min).

Since the corresponding lactate production remained elevated in the patients (S_{II}: −0.84 ± 0.22 µmol/100 g/min; C_{II}: −0.49 ± 0.03, $p < 0.05$), the net amount of glucose taken up by muscle declined (S_{II}: 0.10 ± 0.18 µmol/100 g/min; C_{II}: 0.48 ± 0.08, $p < 0.05$), as could be calculated by comparing the rates of glucose uptake and of lactate and pyruvate release.

In the early postoperative phase oxygen consumption by muscle was slightly, but significantly, reduced as compared to controls (S_I: 0.17 ± 0.01 vol%/100 g/min; C_I: 0.21 ± 0.01, $p < 0.05$). Subsequently, this difference even increased further (S_{II}: 0.14 ± 0.03 vol%/100 g/min; C_{II}: 0.22 ± 0.03; $p < 0.05$). The corresponding arterial oxygen content, however, was comparable between patients and controls (Table 3).

TABLE 4. *Extraction Ratio (%E) by Muscle of AcAc and 3-HOB After a 15-Hour (I) and a 36-Hour Fasting Period (II) in Controls (C; I/N = 10; II/N = 5) and in Postsurgical Subjects (S; I/N = 23; II/N = 8)*

		C	S
AcAc	I	33.1 ± 2.5	38.4 ± 3.8
	II	29.1 ± 2.2	24.0 ± 6.1*
3-HOB	I	24.5 ± 1.9	16.2 ± 2.1†
	II	14.5 ± 1.4*	—

Values represent mean ± SEM.
* Significant difference I *versus* II at p < 0.05.
† Significant difference S *versus* C at p < 0.05.

Discussion

The post-traumatic/postoperative state is characterized by a set of metabolic responses. Catabolism of all substrate stores prevails, as orchestrated by changes in hormonal patterns (increase in plasma levels of catecholamines, corticoids, and glucagon), by immobilization and probably by circulating agents liberated from the site of injury. Thus, proteolysis, lipolysis, and glycogenolysis are accelerated and blood glucose increases due to enhanced hepatic glucose production. Simultaneously, body fuel oxidation shifts toward oxidation of fat, and glucose is being saved for increased demands of

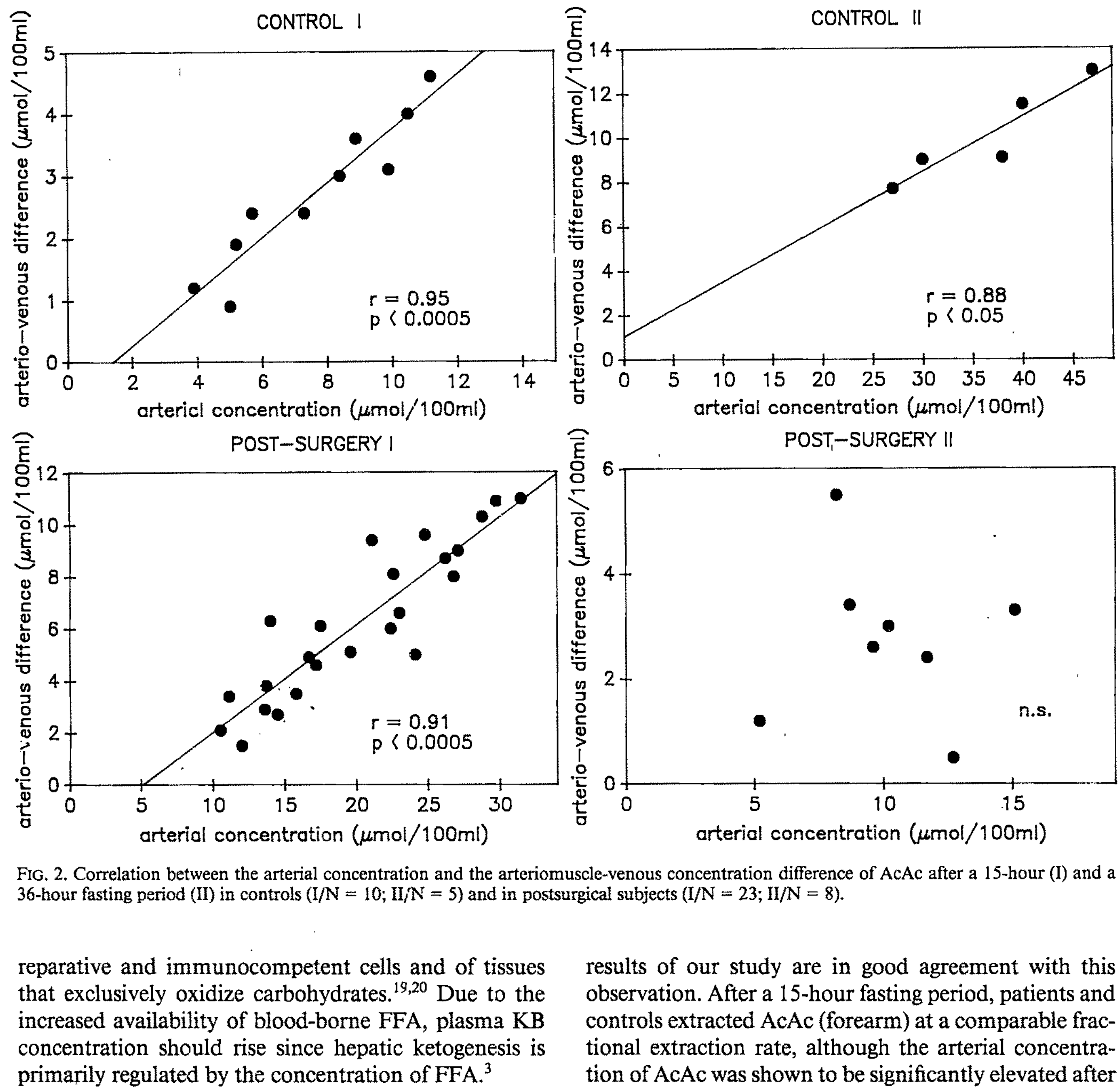

FIG. 2. Correlation between the arterial concentration and the arteriomuscle-venous concentration difference of AcAc after a 15-hour (I) and a 36-hour fasting period (II) in controls (I/N = 10; II/N = 5) and in postsurgical subjects (I/N = 23; II/N = 8).

reparative and immunocompetent cells and of tissues that exclusively oxidize carbohydrates.[19,20] Due to the increased availability of blood-borne FFA, plasma KB concentration should rise since hepatic ketogenesis is primarily regulated by the concentration of FFA.[3]

Our observations in the early postoperative phase are in line with this hypothesis. Three hours after surgery we found twofold to threefold higher levels of KBs compared to controls, following elevated concentrations of lipolytic hormones and FFAs. In the further postoperative course, however, KB concentration in postsurgical subjects significantly fell below that of controls. This well-described phenomenon is probably the result of the antiketogenic action of insulin,[21] alanine,[22] and possibly also of vasopressin[23] compounds, which are all known to increase after surgery.

It has been amply documented that in healthy persons the rate of KB utilization by muscle is directly related to their concentration in blood over a wide range.[1,24] The results of our study are in good agreement with this observation. After a 15-hour fasting period, patients and controls extracted AcAc (forearm) at a comparable fractional extraction rate, although the arterial concentration of AcAc was shown to be significantly elevated after surgery. In addition, a strong linear correlation was apparent between the plasma concentration and uptake of AcAc by muscle (Fig. 2). However, the extraction ratio of 3-HOB immediately decreased after surgery, indicating an impairment of 3-HOB utilization by muscle.

In the further course of fasting, the fractional extraction rate of AcAc and the strong linear correlation between concentration and uptake remained stable in the control subjects, while the arterial concentration of AcAc rose, a finding that is also confirmed by others.[25] On the other hand, in the late postoperative period a diminished extraction ratio for AcAc was observed; a linear correlation between concentration and uptake of AcAc by muscle could no longer be demonstrated (Fig.

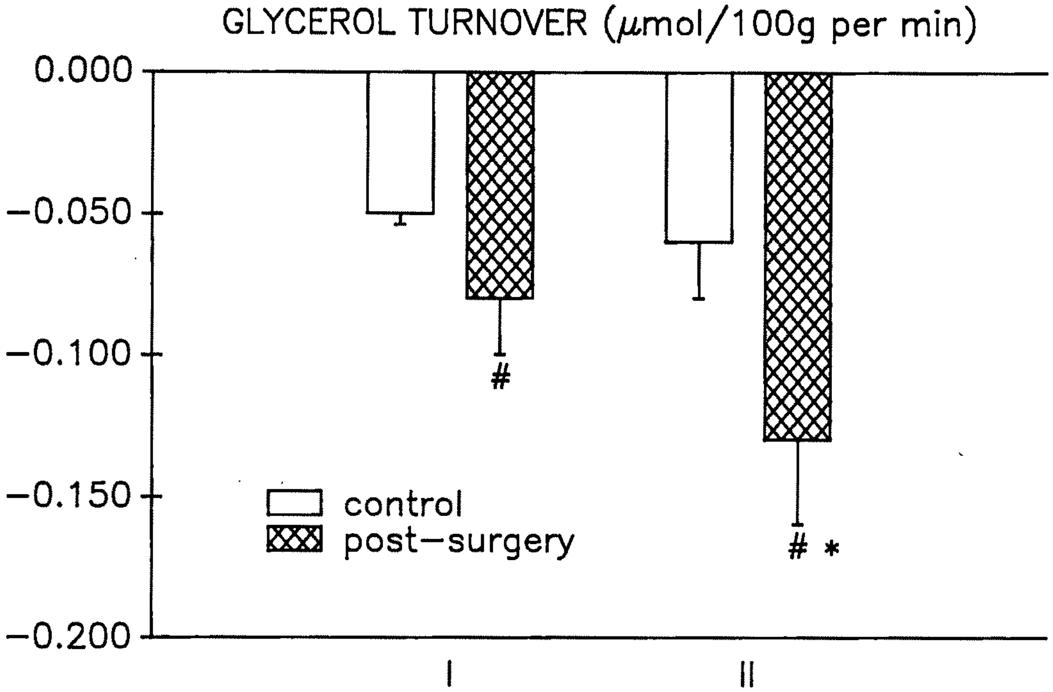

FIG. 3. Production of glycerol by muscle after a 15-hour (I) and a 36-hour fasting period (II) in controls (I/N = 10; II/N = 5) and in postsurgical subjects (I/N = 23; II/N = 8). *$p < 0.05$ *versus* I. #$p < 0.05$ *versus* controls. All values represent the mean ± SEM.

2). Even a net production of 3-HOB by muscle was seen at this time point, underlining the marked alteration of KB metabolism in muscle tissue under these conditions (Fig. 1). Taking into account the low rate of AcAc utilization, a net utilization of KBs was virtually absent. This and the markedly decreased net utilization of glucose pointed to the enhanced use of plasma FFA and of intramuscular substrate stores (fat, protein, glycogen) for energy fuels under these conditions.

The causal sequence of events leading to the peripheral poor assimilation of KB is not completely elucidated by the current studies. However, the potential impact of altered FFA metabolism upon utilization of ketones by muscle deserves further comment. Thus, in our patients we observed a rise in glycerol production by muscle following surgery that was even more pronounced on the first postoperative day, indicating enhanced degradation of muscle triglycerides.[26] Based upon the finding that in surgical patients, who depend mainly on lipid oxidation, combustion of tissue fat stores accounts for the bulk of fat oxidation,[27] the major part of hydrolyzed FFAs appears then to be transferred to mitochondria for beta-oxidation. As can be seen by the increased muscle-venous 3-HOB/AcAc ratio, postoperative skeletal muscle is characterized by a reduced mitochondrial redox state, possibly due to the enhanced beta-oxidation, which would expand the mitochondrial NADH pool.

Therefore, under these conditions, the intramuscular conversion of AcAc to 3-HOB may be strongly favored by shifting the equilibrium of the NADH-linked 3-HOB dehydrogenase reaction toward 3-HOB. In the presence of a rising intracellular concentration of 3-HOB, uptake of 3-HOB by muscle from the blood would decrease; this may explain the depressed extraction ratio of 3-HOB 3 hours after surgery.

However, the reduction of the fractional extraction rate of AcAc, as well as the finding of a net production of 3-HOB by muscle on the first postoperative day, is difficult to interpret by this hypothesis. An additional explanation would be that FFAs and AcAc share a common metabolic pathway, namely, formation of AcAc-CoA and acetyl-CoA.[28] A strongly stimulated degradation of FFA (with the resultant expansion of the AcAc-CoA pool) may directly impair utilization of blood-borne AcAc by inhibiting the reaction of AcAc-degrading enzymes.[1] Since under certain conditions, such as those in severe diabetes, during exercise, or after long-term starvation, KB can also be produced *de novo* in skeletal muscle tissue,[29-31] it cannot be excluded that this phenomenon also contributed to the observed decline in net consumption of KBs.

Consistent with our hypothesis is the fact that in diabetic ketoacidosis insulin administration increases the rate of KB utilization by muscle by inhibiting endogenous FFA release and oxidation.[30] On the other hand, the opposite effect can be produced by a catecholamine infusion into the forearm of diabetic patients, resulting in enhanced muscular glycerol output and a reduced extraction ratio of 3-HOB.[32]

Therefore, it is likely that also during postoperative stress, impairment of KB removal by muscle can be accounted for by the increased utilization of endogenous FFA as a muscle fuel. It appears that, with regard to the depressed KB utilization by muscle 24 hours after surgery, at least this amount of time is required for full stimulation of peripheral FFA utilization. This finding contrasts with the early increase in hepatic ketogenesis following elevation of plasma FFA.

In view of these data one is tempted to speculate about the physiologic importance of KBs and their roles in individual tissues during postsurgical stress. In carbohydrate-deficient states, such as those found after prolonged fasting, KBs may serve as signals of carbohydrate scarcity and initiate glucose sparing mechanisms in peripheral tissues. A similar situation can be assumed in the early postoperative phase when glucose requirements are rapidly increased by demands of reparative and immunocompetent cells and when peripheral combustion of fat alone cannot yet reduce oxidation of glucose sufficiently. During the further postoperative course, muscle tissue is able to substitute utilization of endogenous fat stores for utilization of KBs completely to meet energy requirements and to save glucose. In light of these findings the reduced KB production of the liver at this time may teleologically be reasonable. Furthermore, following severe surgical stress, exogenous KBs are not able to inhibit the overproduction of glucose,[15,33] nor do they exhibit a direct nitrogen-sparing effect.[12,13] Therefore, the development of ketosis in the late postoperative phase would not be anticipated to be as beneficial to the host as the ketosis of starvation.

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Treatment of Dermatofibrosarcoma Protuberans with Mohs Micrographic Surgery

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Ten patients with dermatofibrosarcoma protuberans, all of whom had been treated previously by conventional excisional surgery without success, were treated with Mohs micrographic surgery. A team approach utilizing margin control by Mohs-trained physicians and reconstruction by surgical specialists was employed. Average follow-up exceeds 3½ years, with no recurrences. Microscopically controlled excision appears to be the treatment of choice for dermatofibrosarcoma protuberans.

DERMATOFIBROSARCOMA PROTUBERANS (DFSP) is an uncommon malignant tumor arising *de novo*[1] in the dermis, characterized by local infiltration and indolent progression. While rarely metastasizing,[2–4] this neoplasm is notorious for its propensity to recur even after wide excision. Recurrence rates in various series treated by wide excision are as high as 54%.[5] Current recommendations[1,3,6] call for excision of the tumor with a 3-cm or greater[7] margin of uninvolved skin and underlying fascia. Such generous margins are not possible in all cases, as when the tumor involves the face or distal extremities. Even when managed with wide excision, high recurrence rates of 10–20% have been reported.[3,6]

Since 1979, patients presenting to the Cleveland Clinic Foundation with DFSP have been managed jointly by the Departments of Plastic Surgery and Dermatology, using Mohs micrographic surgery (fresh tissue technique) and postoperative reconstruction. We wish to report ten cases of DFSP treated in this fashion, the largest such series to date. Thus far, no recurrences have been detected on periodic clinical follow-up.

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Methods

In the treatment of large tumors using Mohs micrographic surgery (also called microscopically controlled excision or histographic surgery), the clinically apparent tumor is excised with a conservative margin. A map is drawn of the specimen showing the anatomic orientation of the excised tissue. The specimen is then divided into smaller segments suitable for frozen section processing, and the edges of each smaller segment are color-coded with dyes. These markings are recorded on the anatomic map and can be visualized histologically. Thus, with the Mohs surgical technique the precise anatomic location of each piece can be determined. Horizontal sections are then cut from the bottom of each piece for histologic analysis. For segments located on the periphery of the excisional specimen, a slightly tangential section is cut, establishing a continuous plane from the surface at the edge to the deepest portion of the segment on its interior aspect (Fig. 1). The frozen sections are then stained with hematoxylin and eosin in the routine manner.

This procedure allows the surgeon to simultaneously view the deep and lateral margins of the peripheral segments, as well as the deep margins of the interior segments. This aspect of Mohs surgery, together with the meticulous mapping procedure, constitutes the essential difference from standard margin control and yields significantly higher cure rates.[8] Because the entire margin is examined in this method, residual tumor is precisely identified. The surgeon marks the location of any residual tumor on the map, then returns to the patient to

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remove additional tissue from those exact sites where the margin was positive for tumor. The procedure is repeated in this fashion until no tumor is detected. At this point the wound can be repaired as any other surgical wound. Such precise margin control allows the surgeon to minimize the ultimate size of the wound and yet be more assured of achieving a cure.

As an additional check in this series of patients, pathologic specimens from each case were submitted to board certified dermatopathologists for independent corroboration of the diagnosis.

Case Report

In 1975 a 30-year-old black man (Case 2) had a DFSP of the upper-mid back excised by his local physician, and then received 1000 rads of superficial x-ray to the area after operation. Five years later, a 3-cm diameter tumor was discovered adjacent to the surgical scar. Over a 2-week period, the patient underwent three wide excisions. Upon review of permanent sections after each of the first two of these procedures, margins were found to be involved with tumor. On the third excision, standard margins were clear. Five months later, however, he again noted a new 2.8-cm diameter nodule adjacent to the scar (Fig. 2), and was referred to the Cleveland Clinic Foundation. The patient then underwent Mohs micrographic surgery under local anesthesia. DFSP (Fig. 3) filled all four segments of the initial excision (Fig. 4). A second stage, wider and deeper than the first, revealed tumor in six of ten segments (Fig. 5). A third stage excised from these areas disclosed tumor in one of nine segments (Fig. 6). A fourth excisional specimen in the area of persistent involvement revealed no tumor in either of its two segments (Fig. 7). The resulting 5.5 × 6.4 cm defect (Fig. 8) was closed primarily. The patient has remained free of tumor in 6 years of follow-up.

Results

The case histories of the 10 patients with DFSP treated with Mohs micrographic surgery at the Cleveland Clinic Foundation are summarized in Table 1. Eight patients were male, and all but one (case 1) were less than 37 years old at the time of onset of their disease. Eight patients were Caucasian, one Black, and one Oriental. Seven tumors occurred on the trunk, one on the scalp, one on the cheek, and one on the thumb. All ten patients had been treated with excisional surgery prior to presentation with an average of two prior excisional surgical treatments each, excluding biopsies. Median duration of illness prior to referral for Mohs surgery was 5 years. Six were referred because of recurrence, while four (cases 5, 7, 9, and 10) were referred because of failure to achieve clear margins at surgery.

Seven patients were treated under general anesthesia and three under local. An average of three Mohs stages (excision iterations) per patient was required. Muscle was invaded by tumor in four of the ten cases (cases 5, 6, 7, and 10). In two cases (cases 5 and 7), the tumor extended to periosteum but did not involve bone. Two patients were allowed to heal by second intention, two wounds were closed primarily, two received split-thickness skin grafts alone, and four were repaired by combinations of split-thickness grafts with flaps or partial primary closure.

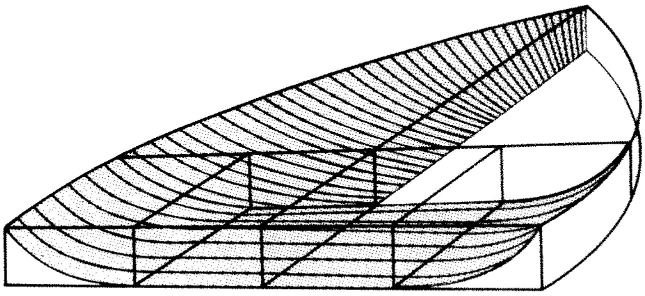

FIG. 1. Sections from each excisional specimen component are cut in such a fashion that a continuous plane is established around the tumor. The pliable nature of fresh tissue allows it to be compressed and stretched as needed to establish planes of section that would not be possible were the tissue rigid.

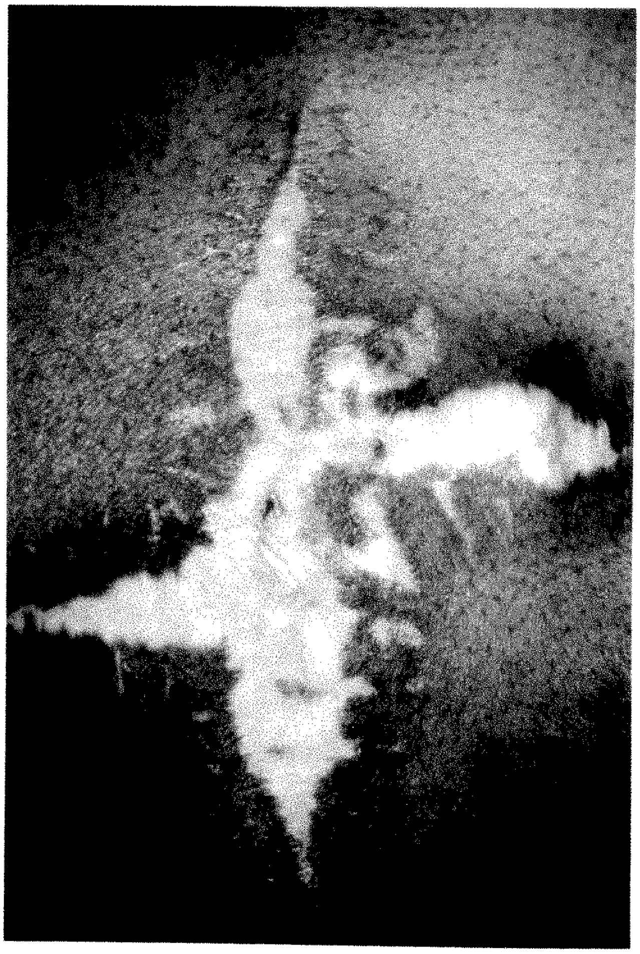

FIG. 2. A 2.8-cm diameter nodule of recurrent DFSP is located between the vertical and upper right arms of the old scar on the mid upper back.

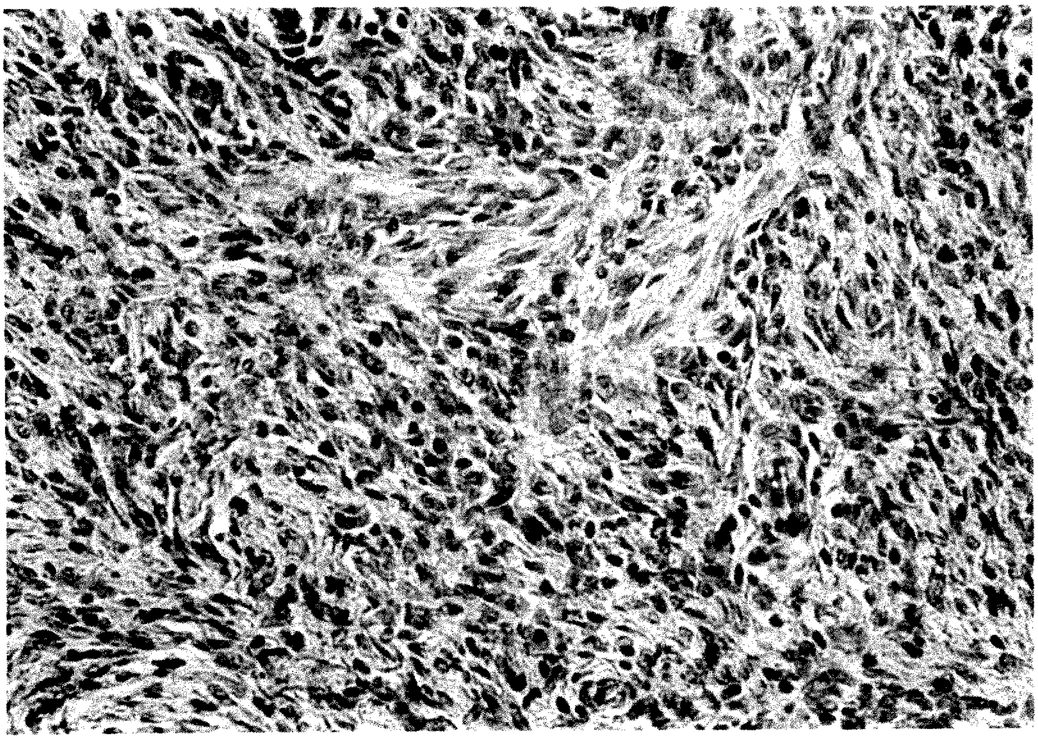

FIG. 3. DFSP is characterized by a storiform pattern of interlacing bands and whorls of fibroblasts, often forming cartwheel-like arrays (hematoxylin and eosin) (original magnification × 20).

The average duration of follow-up in this series of patients is 43 months. Median follow-up duration is 38 months (range: 15–91 months). To date, no evidence of recurrence has been found in any of these patients.

Discussion

DFSP is an unusual tumor, the incidence of which has been estimated at 0.8 cases per one million persons per year.[1] It usually appears in the second through fifth decades,[9,10] but can occur at any age.[4] Most series report a slight male preponderance.[1,6,10] The lesion is most commonly located on the trunk or proximal extremities, but can occur in any location.[4]

Clinically, the lesion appears initially as a dusky indurated plaque, the significance of which is often dismissed by both patient and physician. A history of antecedent trauma is often obtained.[4] The tumor may be

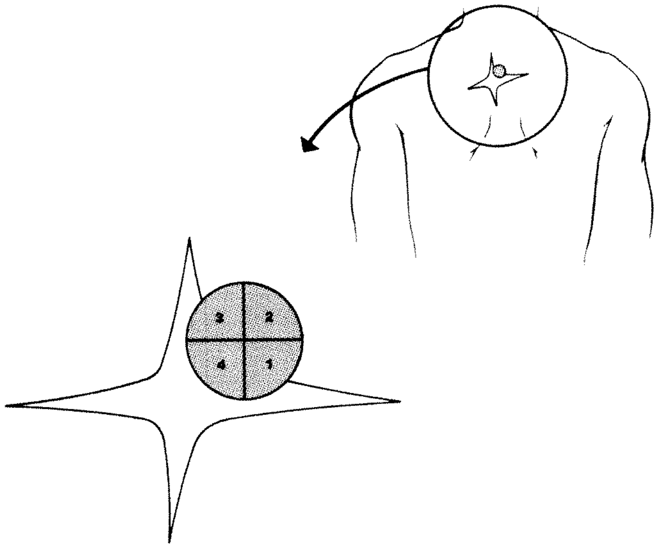

FIG. 4. The stylized Mohs map is shown, with colored dye codings omitted for clarity. All four segments of the initial excision were filled with DFSP, as indicated by shading.

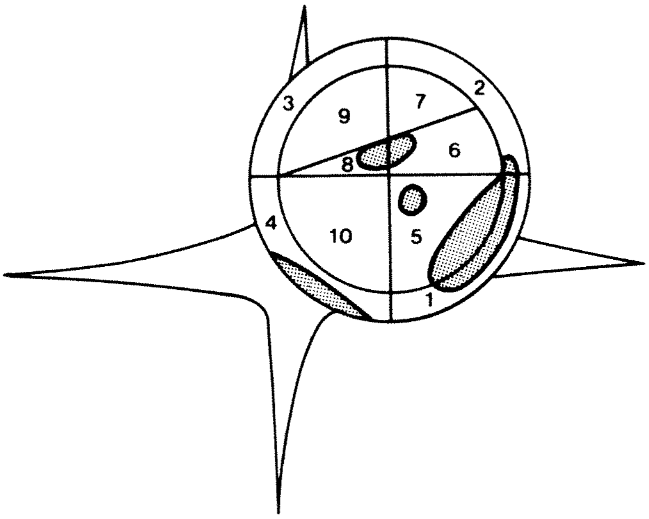

FIG. 5. The second excision was wider and deeper than the first, and disclosed tumor at the margin in six of ten segments.

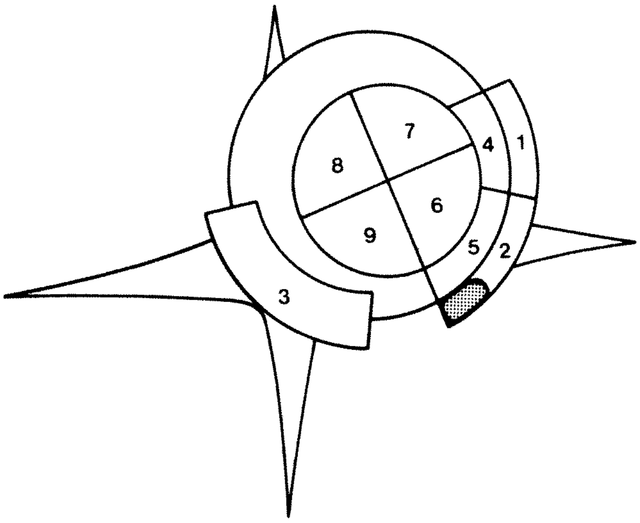

FIG. 6. The third excision, restricted to the areas positive for tumor in the second, revealed tumor at the margin in one of nine segments.

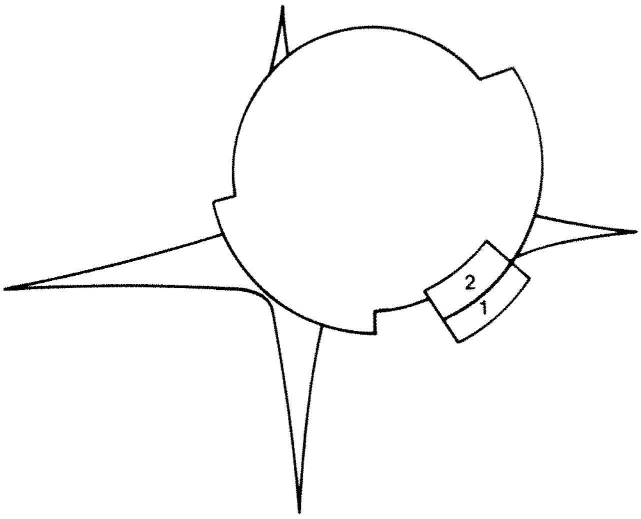

FIG. 7. The final excisional specimen was free of tumor in both segments processed.

flesh-colored, bluish-red, reddish-brown, or yellow in color. In time, sometimes decades, the tumor develops a nodular or multinodular quality and may become symptomatic and ulcerate. Neglected lesions may be quite large, as great as 20 cm in diameter[1,10] clinically, but even large tumors are usually not bound down to underlying noncutaneous structures. In advanced stages, the tumor may invade fascia and muscle. While pulmonary and nodal metastases do occur,[6,7,11] such biologic behavior is rare. The incidence of metastases has probably been overestimated by virtue of the inadvertent inclusion of tumors now defined as malignant fibrous histiocytoma[2] or other soft tissue malignancies[4] in older series reporting metastatic DFSP.

Histologically, DFSP is characterized by a storiform pattern created by spindle-shaped cells arranged in cartwheel-like arrays about collagenous centers.[4] The interlacing bands and whorls of fibroblasts often fill the entire reticular dermis and extend into subcutaneous fat. The center of DFSP tends to be more cellular than the pe-

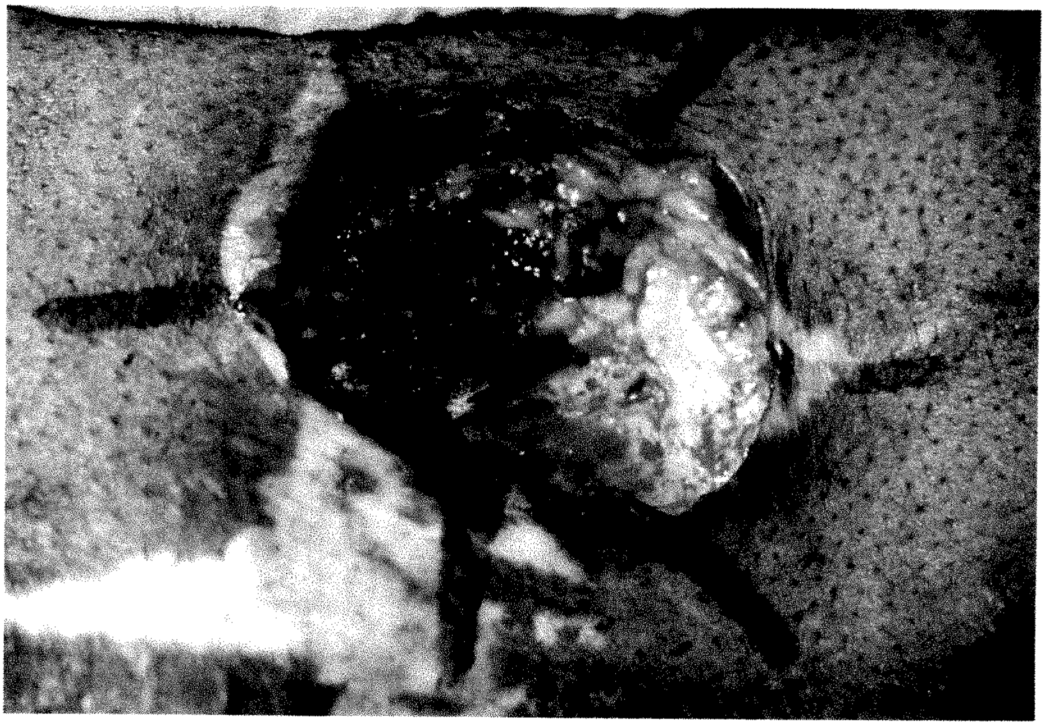

FIG. 8. The final operative defect measured 5.5 × 6.4 cm and was closed primarily.

TABLE 1. *Summary of Cases*

Case No.	Age at Mohs Surgery (yr)	Tumor Location	No. of Prior Excisions (Excluding Biopsies)	Repair	Months of Follow-up
1	68	Chest/neck	2	STSG,* myocutaneous flap	91
2	35	Back	4	Primary closure	74
3	38	Back	4	Partial primary closure, STSG	47
4	20	Chest	1	None	42
5	22	Scalp	2	STSG	39
6	43	Cheek	4	STSG, then rectus abdominis free flap	37
7	18	Shoulder	1	STSG	34
8	39	Hip	2	Flap, STSG	29
9	35	Thumb	1	None	24
10	5	Back	2	Primary closure	15

* Split-thickness skin graft.

riphery, where cells appear more mature and are associated with collagen.[4] Large numbers of mitotic figures are usually not seen, nor is cytologic atypia usually found. While the cellular origin of this tumor remains controversial, evidence favors the fibroblast.[12]

The nodular quality of DFSP gives the clinician an erroneous impression of circumscription,[4,12] which results in frequent treatment failures. The main body of the tumor gives off multiple pseudopod-like projections of neoplastic cells, which may extend 3 or more cm beyond the tumor proper, infiltrating between normal collagen bundles both laterally and deep. These finger-like projections of tumor are microscopic in size and cannot be appreciated clinically. For the same reason, these extensions can be missed by any histologic sectioning technique (including vertical step sectioning) that does not examine the entire undersurface and lateral margins of the excisional specimen. Failure to excise all of these projections is presumed to be the major reason for the high rate of recurrence noted with this tumor.[10]

In 98 cases studied by Taylor and Helwig, a 49% rate of recurrence was found, nearly 40% of which recurred during the first year and 75% within 3 years following surgery.[4] In Hajdu's series of 119 cases, 54% recurred after wide excision, most within the first year. Of 17 cases treated by Pack and Tabah,[10] 24% recurred. Similarly, one fourth of those treated by Burkhardt et al.[9] recurred. Rowsell et al.[13] reported five cases, all of which had to be returned to surgery when margins were found to be involved. Two of these patients required two additional surgical procedures each, and one patient required three additional surgical procedures, in spite of the authors' technique of taking an average 2.7 cm margin of clinically uninvolved skin and subcutaneous tissue at the first re-excision.

McPeak et al.[6] reported an 11% recurrence rate in 27 patients treated with a 3-cm margin of clinically uninvolved skin, down to and including fascia. Seventy-five per cent of the recurrences in their overall series of 86 patients was noted in the first 2 years. Roses et al.[3] used 3-cm margins in ten patients and reported a 20% recurrence rate, while Bendix-Hansen et al.[1] took 3-cm margins in seven patients and had no recurrences.

While recurrences are usually noted within 3 years,[3,4] late recurrences have been noted at 19 years[10] and 20 years.[4] However, although late recurrence is uncommon, this phenomenon must be kept in mind when assessing the efficacy of any proposed treatment for DFSP.

Mohs micrographic surgery was devised more than 50 years ago by Frederic E. Mohs, M.D. at the University of Wisconsin.[8] In Mohs' original fixed tissue technique, a chemical paste of zinc chloride was applied to cancerous tissue *in situ,* and subsequently the tissue was excised bloodlessly, mapped, and processed utilizing horizontal frozen sections to achieve total margin control. While the fixed tissue technique is still used in selected applications[8] today, such as highly vascular tumors, bone tumors, or neoplasms with higher metastatic potential, it has largely been replaced since the early 1970s by the fresh tissue technique, which does not utilize zinc chloride paste.

Mohs micrographic surgery is well suited to the treatment of neoplasms that tend to invade aggressively but locally, and have low rates of metastasis. Its most frequent application is in the treatment of recurrent basal cell carcinomas, large or morpheaform primary basal cell carcinomas, and midfacial or periauricular basal cell carcinomas. It is also useful for squamous cell carcinoma and squamous cell carcinoma *in situ,* sebaceous carcinoma, microcystic adnexal carcinoma, cutaneous adenoid cystic carcinoma, Merkel cell tumors, malignant fibrous histiocytoma, and extramammary Paget's disease.

The precise margin control made possible by Mohs surgery enables the removal of microscopic-sized extensions of tumor while conserving the maximum possible amount of normal tissue. It eliminates the guesswork inherent in excising tumors by arbitrary margin guidelines, such as the 3-cm guideline previously recommended for DFSP.[3] This advantage is especially appreciated when the tumor is located on or near functionally or cosmetically important structures such as the hand or face. Furthermore, the confidence generated by total margin control permits definitive plastic repair immediately upon conclusion of the Mohs procedure. This tissue-sparing feature also allows the use of wound repairs that would not be possible if the lesion were excised with 3-cm or greater margins, which typically necessitates split-thickness skin grafts.[6] The tissue conservation permitted by Mohs surgery even permits some smaller wounds to be closed primarily or to be allowed to heal by second intention.

Our team approach capitalizes on the margin control capabilities of Mohs-trained physicians and on the operative talents of surgical specialists. Small primary tumors can be excised, checked for positive margins, and repaired under local anesthesia in the outpatient surgical suite. The inpatient operating room and general anesthesia are utilized when indicated to eliminate the discomfort of local anesthesia, to reduce the risks of lidocaine toxicity, and to make use of monitoring and fluid replacement capabilities. In this setting, the Mohs surgeon can assist the surgical specialist by orienting and mapping excised tissue, and by rapidly checking all margins histologically with the Mohs technique. This modification of the traditional Mohs procedure has been shown to conserve valuable normal tissue in the surgical treatment of cutaneous tumors of the head and neck.[14]

Some authors have remarked that soft tissue neoplasms can be more difficult to read histologically with tissue processed using frozen sections.[12,15] Like Peters et al.,[16] we have experienced no difficulty in differentiating benign tissue from that involved with DFSP on standard Mohs sections.

To date, there are no reported instances of recurrence of DFSP following Mohs micrographic surgery. Mohs himself reported[17] five cases treated by the fixed tissue technique and two by the fresh tissue technique, all without recurrence after more than 5 years. Robinson reported four cases treated by the Mohs technique, with no recurrence after 5 years of follow-up.[12] Peters et al.[16] excised a facial DFSP with a modification of the Mohs procedure and had no recurrence 3½ years later.[18] Hess et al.[18] treated a myxoid DFSP of the chest with Mohs micrographic surgery and had no recurrence at follow-up 18 months later. Mikhail and Lynn[19] used Mohs surgery in two cases and had no recurrence in either more than 5 years later.[12]

The unusually high percentage of cases with muscle invasion (40%) reported here reflects an advanced state of disease in this series of patients having persistent or recurrent tumors. Given the possibility of late recurrence, it cannot be stated with absolute certainty that a cure has been effected in any of these cases. However, our average and median follow-up durations of 43 and 38 months, respectively, now exceed the 3 years, that constitute the period of greatest likelihood of recurrence.[3,4,6] Because of its inherent ability to spare normal tissue and yet to completely eradicate the tumor, Mohs micrographic surgery appears to be the treatment of choice for DFSP.[18,20]

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Antibiotic Use During Major Head and Neck Surgery

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The appropriate use of prophylactic antimicrobial therapy in patients undergoing major contaminated surgery is an important issue for the head and neck surgeon. A series of five sequential, prospective, randomized, double-blind clinical trials of antibiotics for patients undergoing major contaminated oncologic head and neck surgery are reviewed and summarized. The information generated from the study of these 547 patients indicates that a number of drugs or drug combinations have similar efficacy when employed in adequate dosage. The bacteriologic spectrum of the prophylactic drug should include oral microflora, especially anaerobic bacteria. The administration of antibiotics effective against gram-negative aerobic bacteria may be unnecessary. Perioperative antibiotic administration should be initiated prior to surgery. To date, no evidence exists to support prolonged administration of antibiotics beyond the first 24 hours following surgery.

SURGEONS HAVE RELIED upon the administration of perioperative antibiotics to help reduce the incidence of postoperative wound infection. In a landmark study, Burke[1] demonstrated that the administration of antibiotic is maximally effective in preventing bacterial invasion when the antibiotic is administered prior to bacterial contamination. Administration of antibiotic 3 or more hours after bacterial contamination was ineffective in preventing bacterial invasion. This principle has been confirmed in human studies and is accepted today.[2-5]

The issue of prophylactic antimicrobial therapy for patients undergoing major head and neck surgery continues to produce some confusion. As a result, we present a brief review of recent clinical trials from our institution, which addresses issues of relevance to the surgeon. In a series of prospective, randomized clinical trials conducted in patients undergoing major oncologic head and neck surgical procedures, we have attempted to better define the spectrum of antimicrobial agents that have efficacy in preventing postoperative wound infections and to determine the optimal duration that these agents should be administered.

When contamination with oropharyngeal secretions does not occur, antibiotics are not required in patients undergoing major head and neck procedures. Clean procedures, such as thyroidectomy, parotidectomy, submandibular gland excision, or isolated radical neck dissection, are associated with postoperative wound infection of less than 2%.[6] Administration of antibiotic prophylaxis under these circumstances has not been demonstrated to reduce the risk of postoperative wound infection.

On the other hand, when major head and neck surgical procedures are contaminated by exposure to oropharyngeal secretions, the risk of a postoperative wound infection significantly increases. Wound infection rates of 28–87% have been reported.[7,8] This broad range may reflect variations in the magnitude of the procedures undertaken and differences in the definition of postoperative wound infection. It is now agreed that administration of perioperative antibiotics to patients undergoing contaminated head and neck procedures is required. In a prospective, randomized, placebo-controlled trial, seven of nine patients (78%) receiving a placebo from our institution developed a postoperative wound infection.[5]

Methods

These clinical trials were undertaken in a prospective, randomized, and double-blind fashion. Only patients

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scheduled to undergo contaminated (skin to mucosa) oncologic surgical procedures were eligible. Patients undergoing transoral procedures or procedures in which the skin was not closed (*e.g.*, maxillectomy or planned fistula) were ineligible. During the course of the surgical procedure, the standard tenets of surgical antisepsis were followed and no major break in antiseptic technique occurred. Prior to randomization, patients were stratified by computer for factors that potentially affect the incidence of postoperative wound infection. These parameters included stage of disease (stage IV *vs.* stage III or less), timing of tracheotomy (anticedent tracheotomy *vs.* concurrent tracheotomy), exposure to radiation therapy (prior radiation *vs.* no radiation therapy), closure technique (primary closure *vs.* myocutaneous flap reconstruction), and surgical procedure (laryngectomy *vs.* other head and neck procedures).

Antibiotic Study I

In our first study, patients were randomly assigned to receive cefazolin (Kefzol®) alone (500 mg) *versus* clindamycin (Cleocin®) (600 mg) plus gentamicin (1.7 mg/kg).[9] The study regimen was administered intravenously 1 hour before operation and continued after surgery three times a day for either 1 or 5 days postoperatively.

Antibiotic Study II

The second study evaluated the efficacy of third-generation cephalosporin antibiotics in the prevention of postoperative wound infections.[5] Patients were randomly assigned to receive either cefoperazone (Cefobid®) (2 g), or cefotaxime (Claforan®) (2 g). This study was placebo-controlled. In each case, the study drug was administered intravenously 1 hour prior to surgery and continued every 8 hours for a total of four doses. The last drug administered was at 24 hours after surgery.

Antibiotic Study III

Prospective, randomized trials in other surgical fields have not consistently demonstrated increased efficacy of third-generation cephalosporins when compared to first-generation cephalosporins in the prevention of postoperative wound infection.[10–14] We theorized that the observed lack of efficacy of cefazolin in prophylaxis in our initial antibiotic trial may have been dose related in that the 500 mg dose may have been inadequate. Therefore, a second cefazolin trial was developed.[15]

Patients were randomly assigned to receive cefazolin (Kefzol®) (2 g) or moxalactam (Moxam®) (2 g). Once again, all antibiotics were begun 1 hour before operation and continued every 8 hours for a total of four doses.

Antibiotic Study IV

Gram-negative aerobic bacteria are frequently isolated from secretions obtained from postoperative head and neck wound infections. This is paradoxical in that gram-negative aerobic organisms are not normally inhabitants of the mucosal surfaces of the upper aerodigestive tract. To determine if the observed gram-negative aerobic bacteria were merely colonizing, preexistent wound infections rather than pathogenic, we undertook another study.[16] Patients were randomly assigned to either clindamycin (600 mg) *versus* clindamycin (600 mg) plus gentamicin (1.7 mg/kg). Clindamycin is active against gram-positive *cocci* and anaerobic bacteria, but not aerobic gram-negative *bacilli.* Thus, the clindamycin alone regimen lacked coverage against aerobic gram-negative *bacilli,* a notable omission when compared to previously established regimens of cephalosporin agents. In each case, antibiotics were administered intravenously beginning 1 hour preoperatively and continued every 8 hours for four doses (1 day).

Antibiotic Study V

It was speculated that longer duration of antibiotic administration may be a factor for a small subpopulation of patients undergoing major head and neck surgery. In our experience, patients at greatest risk for postoperative wound infection were those patients undergoing pectoralis major myocutaneous flap reconstruction after resection of an advanced stage carcinoma. To test the hypothesis that this subgroup of patients undergoing flap reconstruction would benefit from prolonged administration of antibiotics, another study was developed for patients in whom pectoralis major myocutaneous flap reconstruction was anticipated.[17] In a multi-institutional, prospective randomized trial, these patients were randomized to cefoperazone (2 g) for either 1 or 5 days postoperatively. In each case, the antibiotic was initiated 1 hour preoperatively and continued every 12 hours for the duration of the study. Patients randomized to 1 day of antibiotic received placebo on days 2, 3, 4, and 5.

Results

Antibiotic Study I

One hundred seven patients were randomized into this study. Wound infection developed as follows: cefazolin, one day (33%); cefazolin, five days (20%); clindamycin plus gentamicin, one day (7%); clindamycin plus gentamicin, five days (4%). These data demonstrated a statistically significant advantage using the drug combination clindamycin plus gentamicin *versus* cefazolin alone. The rate of postoperative wound infection for the patients receiving antibiotic for five days was not signifi-

TABLE 1. *Effect of Drug and Dose on Wound Outcome*

Drug	Dose	No. of Doses	Patients	Infections (%)	p Value
Placebo	—	—	9	7 (78)	<0.001
Cefazolin	500 mg	4	21	7 (33)	<0.05
Cefazolin	2 g	4	59	5 (8.5)	
Clindamycin	600 mg	4	52	2 (3.4)	
Clindamycin	600 mg	—	—		
Gentamicin	1.7 mg/kg	4	81	4 (4.9)	
Cefoperazone	2 g	4	39	4 (10)	
Cefatoxime	2 g	4	32	3 (9)	
Moxalactam	2 g	4	59	2 (3.4)	

cantly different from the patients receiving antibiotic for one day ($p > 0.05$).

Antibiotic Study II

Eighty-seven patients were enrolled. Wound infection developed in seven of nine patients (78%) assigned to placebo. This arm of the study was subsequently closed. Three of these patients experienced bacteremia. In each case, the organism identified was an anaerobic bacteria that was simultaneously identified in material taken from the wound.

Wound infections were encountered in 10% and 9.4% of patients receiving cefotaxime and cefoperazone, respectively. The observed rate of wound infection was not statistically different from the infection rate observed in patients receiving clindamycin plus gentamicin.

Antibiotic Study III

One hundred eighteen patients were enrolled. Wound infections were seen in five patients (8.5%) receiving cefazolin and two patients (3.4%) receiving moxalactam. These differences were not statistically significant ($p > 0.05$).

Antibiotic Study IV

One hundred four patients were enrolled. Wound infection occured in only two patients (3.4%) receiving clindamycin alone and in two patients (3.4%) receiving clindamycin plus gentamicin.

Antibiotic Study V

One hundred forty-two patients were enrolled 109 of whom underwent flap reconstruction as anticipated. The majority of the remaining 33 patients did not undergo flap reconstruction as a result of intraoperative evaluation.

Fifty-three patients received one day of antibiotic prophylaxis. Infection developed in 10 (18.9%). Postoperative wound infection developed in 14 of 56 (25%) of patients who received 5 days of perioperative prophylactic antibiotics ($p > 0.05$).

Conclusion

The combined results of five prospective, randomized, and double-blind clinical trials undertaken in 547 patients undergoing major contaminated oncologic head and neck surgery can serve as a basis for rational decision-making in this controversial arena.

First, it appears that a number of drugs or drug combinations (Table 1) may have similar efficacy in the prevention of postoperative wound infection when administered in adequate therapeutic dosage. We caution that while these studies do not show significant differences among the agents used, these data do not necessarily indicate that these agents are of equal value. Studies with much larger sample sizes would be required to satisfy the statistical requirements for such a claim.

Second, the spectrum of antibiotics used for oncologic head and neck surgery must include that of anaerobic microflora of the oral cavity. The most important group of oropharyngeal anaerobic bacteria that are potential pathogens include *fusobacterium, bacteroides,* and *peptostreptococcus* species. While the issue of coverage against aerobic gram-negative bacteria is not definitively settled, it appears that routine prophylactic coverage for these organisms is not necessarily indicated.[7,11]

Third, these data fail to demonstrate improved efficacy for antibiotics administered greater than 24 hours after operation. This observation is in keeping with observations made by other investigators studying head and neck patients.[18,19] We acknowledge that there may exist a subgroup of head and neck patients who may benefit from more prolonged administration of perioperative antibiotic prophylaxis. Further evaluation of patients undergoing skull base surgery, the use of free flaps, and mandibular reconstruction must be undertaken before this issue can be more precisely addressed.

In each of these studies, the antibiotic was administered intravenously 1 hour prior to surgery in keeping with the tenets established by Burke.[1] Failure to administer the antibiotic prior to contamination may render prophylaxis ineffective.

In summary, these comprehensive studies provide a rational basis for selection of antibiotics to be used as prophylaxis for contaminated oncologic head and neck surgery. Other factors including relative costs and potential side effects of these agents can be taken into consideration and would vary with the patient population, hospital situation, and experience of the surgeon.

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Book Reviews

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Tissue Plasminogen Activator in Thrombolytic Therapy. 264 pp. Burton E. Sobel, Désiré Collen, Elliott B. Grossbard. New York: Marcel Dekker, Inc. 1987. $55.00.

One of the most remarkable of recent achievements in medicine has been the development of *tissue plasminogen activator* and its application as a thrombolytic agent in the management of a variety of thrombotic disorders. The editors of this authoritative monograph have summarized the current data concerning this impressive activator and presented it in a logical, thoughtful, and effective manner. The clinical use of *recombinant* tissue plasminogen activator (rt-PA) was initiated with the treatment of the first patient in February 1984, and in this text the data concerning management of more than 3000 patients treated in the United States, Europe, Australia, Canada, New Zealand, and Japan are summarized. The text proceeds through a review of pharmacokinetics, biological activity, and clinical pharmacology of tissue plasminogen activator with special attention to rt-PA.

In 1980, Rijken first produced 1 mg of t-PA from 5 kg of human uterine tissue using a special procedure. Working with Collen, Rijken later utilized a modification of this process to purify gram quantities of t-PA from a melanoma cell line. Although these techniques were tedious with a relatively low yield, nevertheless, a sufficient amount of highly purified t-PA was produced for extensive biological, physiological, and biochemical study. In 1981, Weimar and Collen reported two patients with renal vein thrombosis treated successfully with t-PA, and this report stimulated scientists at Genentech to successfully clone and express the human t-PA gene in Chinese hamster ovarian cells in tissue culture, the gene product called recombinant human tissue type plasminogen activator or rt-PA. In 1983, seven patients with acute myocardial infarction were treated with melanoma-derived t-PA, and six exhibited coronary thrombolysis. This prompted the formulation of a protocol for the multicenter trial of t-PA in the treatment of acute myocardial infarction with participation of investigators at Johns Hopkins, the Massachusetts General Hospital, and Washington University together with Genentech scientists. In 1984, the National Heart, Lung and Blood Institute (NHLBI) began a pilot trial with rt-PA, and the results confirmed those found by the earlier Genentech-sponsored protocol. Although a randomized double-blind trial comparing rt-PA with streptokinase was initiated by the NHLBI, it was not completed due to the fact that it became obvious that rt-PA was superior.

This is a very valuable monograph for all involved in the management of clinical conditions requiring fibrinolytic therapy. It is remarkable how rapidly rt-PA was developed and how successful it has been applied clinically. This text is essential for all those involved in investigative and clinical aspects of those disorders leading to intravascular thrombosis and its sequelae.

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Essentials of Surgery. 1272 pp. David C. Sabiston, Jr. Philadelphia: W. B. Saunders Co. 1987. $39.95.

As Dr. Sabiston stated in his Preface, this textbook was initiated to meet a "need for a more compact text" for medical students based on the established standards of the highly successful *Textbook of Surgery: The Biological Basis for Modern Surgical Practice.* Although this textbook is about half the size of the standard text, it is fairly comprehensive, including surgical specialties such as cardiothoracic surgery, neurosurgery, plastic and maxillofacial surgery, orthopedics, otolaryngology, gynecology, urology, and pediatric surgery.

The first chapter in the book, appropriately entitled "Milestones in Surgery," succinctly chronicles the major historical developments in surgery. In addition, the historical development of the subject is briefly described in each section. This refreshing presentation of historical developments in surgery, particularly for medical students, is a reflection of Dr. Sabiston's scholarly interests.

Throughout the text, basic principles and fundamental concepts are emphasized but are elaborated on in chapters dealing with homeostasis and shock, fluid and electrolyte management, nutrition and metabolism in surgical patients, wound healing and management, surgical infections and choice of antibiotics, and anesthesia. A chapter is devoted to appropriate surgical consideration of virtually every organ in the body. Each chapter includes selected references with a short description of the contents. Appropriate illustrations of technical procedures, as well as tables, graphs, and algorithms, are generously sprinkled throughout the text to enhance the clarification of some of the more complex problems. At the end of the book is a most useful chapter on Normal Values, which is concerned with normal or reference values for the most commonly performed laboratory tests both in conventional units and in S.I. units (International System of Units).

In a thorough review of this textbook, I observed only one departure from a comprehensive, although often succinct, consideration of surgical problems, and that was in the section on Arterial Aneurysms in the chapter on The Arterial System. The only reference to aneurysms of the thoracic aorta is a statement that they may occur and that cystic medial necrosis is a common predisposing factor to dissecting aneurysms. Similarly, only a passing reference is made to dissection in the chapter on Acquired Diseases of the Aortic Valve. Yet, aneurysm of the abdominal aorta is adequately discussed in the chapter on The Arterial System. It is almost captious to make this comment since obviously some judgments had to be made in condensing the text.

Although this textbook is directed primarily toward providing "information expected to be acquired by medical students prior to graduation," in the opinion of this reviewer, it is highly recommended for residents training in surgery and even for practicing surgeons. It provides an excellent and authoritative quick reference to virtually all conditions requiring surgical consideration.

As might be expected from the author who is recognized not only for his investigative and clinical capabilities but also for his scholarly and literary qualities, the textbook material is highly readable, despite a number of different contributors.

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Current Therapy in Critical Care Medicine. 355 pp. Joseph E. Parrillo. Philadelphia: B. C. Decker, Inc. 1987. $49.00.

WITH THE RECOGNITION OF the increasing complexity of and the unique body of knowledge associated with intensive care, there has been a proliferation of textbooks and monographs dealing with various aspects of critical illness. Some have focused on specific topics, such as cardiopulmonary pathophysiology and support, whereas others have attempted to deal with the full panoply of issues confronting those who care for critically ill patients. This volume is of the latter category. It is intended to provide the "active . . . critical care physician" with current therapeutic information. Like most similar texts, it is multiauthored, and, as with so many other texts, that multiauthorship is both a strength and a weakness.

The format of the book is reasonable, although it is not clear why such topics as tracheal intubation, bronchoscopy, and mechanical ventilation were included in the section on Diagnostic and Therapeutic Techniques rather than the Pulmonary section. A more serious problem with the format is that the editor has chosen to omit bibliographic references, even for areas that are highly controversial (Ethical Issues) or very technical but briefly summarized (Burns and Electical Injuries). The result of this omission is that the reader who wishes to increase the depth of his knowledge on a particular subject is forced to turn to a different text for source material.

Although there is excellent treatment by internationally recognized experts of some topics (Bedside Hemodynamic Monitoring, Interstitial Lung Disease), other topics are less well covered. Moreover, there is a lack of consistency between the treatment of specific issues given in different chapters. For example, in a discussion of weaning from mechanical ventilation, one chapter advocates T-piece trials, whereas another does not. Elsewhere, one author advocates the use of colloid for volume resuscitation; in a different chapter discussing the same subject, crystalloid therapy is advised. There is no attempt by the editor to reconcile these differences.

This book has a reasonable idea as its premise. It is unfortunate that it frequently leaves the reader with many unanswered questions.

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Seattle, Washington

Surgical Management of Morbid Obesity, Vol. 12 in the series **Science and Practice of Surgery.** 320 pp. Ward O. Griffen, Jr., Kenneth J. Printen. New York: Marcel Dekker, Inc. 1987. $79.75.

A RECENT VISITING PROFESSOR from China, when asked about his most significant impression about the United States, replied readily that he was most struck by the large number of fat Americans. His observation is readily confirmed by a visit to any shopping mall; morbid obesity has become a common and almost epidemic disorder. The enormous excess of weight is a clear health hazard; the disease is associated with a high incidence of diabetes mellitus, hypertension, vascular disease, biliary disease, arthritis, malnutrition, and sharp limitations of functional effectiveness.

The small book, *Surgical Management of Morbid Obesity,* presents an excellent and concise summary of our current approaches to this serious disease. The book was written by some of the pioneers who recognized years ago that morbid obesity is an illness serious enough to warrant surgery and who then went on to design and test a broad variety of operations. The development of the current procedures has not come easily; an interesting facet of the book is its excellent presentation of the history of bariatric surgery.

Under the obviously excellent editorial control of Griffen and Printen, such well-known obesity surgeons as Mason, Halverson, and Scopinaro present not only their approaches in detail, but also report a treasure of data from their experience and share useful hints about patient management. With the exception of Scopinaro's contribution, which is a bit long, the remainder of the chapters are unusually concise, well organized, and informative.

The book is not only an essential reference for anyone involved in bariatric surgery, it is also a textbook of gastric physiology. Doctors Griffen and Printen deserve our thanks and our congratulations for this important contribution to the surgery of morbid obesity.

WALTER J. PORIES, M.D.
Greenville, North Carolina

Atlas of Clinical Gastroenterology. 283 pp. J. J. Misiewicz, C. I. Bartram, P. B. Cotton, A. S. Mee, A. B. Price, R. P. H. Thompson. Philadelphia: Lea & Febiger. 1987. $110.00.

THIS BOOK, *Atlas of Clinical Gastroenterology,* which arrived on my desk for review a week or so ago, is no ordinary atlas by any stretch of the imagination. Rather, it is an informative, comprehensive comparison of normal and diseased structures as depicted by beautiful photographs of gross microscopic and ultramicroscopic anatomy displayed in luxuriant colors and by conventional x-rays and scans. Anatomic diagrams help the readers' understanding of the figures. The first part of each section is an identifiable introduction to the normal organ structure, innervation, and function leading to an illuminating display of gastrointestinal and hepatobiliary pathology. It is so clearly well done that comparison easily becomes contrast.

For each organ, the authors have described all important diseases and have included lesser ones, which lend themselves to beautiful illustrations (*e.g.*, abetalipoproteinemia, intestinal lymphangiectasia). Especially helpful in this organ recital are the diagrams that accompany practically all of the illustrations of gross pathology, x-rays, scans, etc.

The text is brief (as it should be for the purposes of such a volume), clear, and to the point. Collectively, it encompasses a lot of information. A special value of the work, of course, is that it comprehensively correlates findings of the most up-to-date techniques for diagnosis with the beautiful illustrations of gastrointestinal pathology as demonstrated by new scanning techniques, endoscopy, histochemistry, and ultramicroscopy. Slides of all this material undoubtedly comprise the best teaching collection of gut and liver pathology extant.

Especially valuable are the pictorial and descriptive evolutions of some of the more important diseases. Thus we see the progressive changes from benign colon adenoma to invasive cancer, from diverticula to diverticulitis, and from uncomplicated duodenal ulcer to bleeding or perforation. The endoscopic illustrations will especially delight teachers and the students of gastroenterology studying the gross differences between benign and malignant tumors, between various forms of vascular anomalies, and between ischemic and inflammatory ulceration and necrosis.

We are indebted to Dr. J. J. Misewicz and his authoritative colleagues who have given us the best illustrations and descriptive summaries of normal gut and liver anatomy and physiology, and of their clinically important diseases. Their demonstration of the contributions of modern techniques to diagnosis of disease and to understanding correlations of normal structure and function and of disease and dysfunction, will serve as an effective introduction to gastroenterology. The *Atlas of Clinical Gastroenterology* is a major effort and it will be a work to which we all will refer again and again.

MARVIN H. SLEISENGER, M.D.
San Francisco, California

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   Anonymous. Epidemiology for primary health care. Int J Epidemiol 1976; 5:224–5.

Books and Other Monographs

3. Personal Author(s)

   Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

4. Corporate Author

   American Medical Association Department of Drugs. AMA drug evaluations. 3rd ed. Littleton: Publishing Sciences Group, 1977.

5. Editor, Compiler, Chairman as Author

   Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

6. Chapter in Book

   Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–71.

7. Agency Publication

   National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968–June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72-1036).

Other Articles

8. Newspaper Article

   Shaffer RA. Advances in chemistry are starting to unlock mysteries of the brain: discoveries could help cure alcoholism and insomnia, explain mental illness. How the messengers work. Wall Street Journal 1977 Aug 12:1(col. 1), 10(col. 1).

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COMMONLY USED APPROVED ABBREVIATIONS

Standard Units of Measurement

Term	Abbreviation or Symbol
ampere	A
ångström	Å
barn	b
candela	cd
coulomb	C
counts per minute	cpm
counts per second	cps
curie	Ci
degree Celsius	°C
disintegration per minute	dpm
disintegration per second	dps
electron Volt	eV
equivalent	Eq
farad	F
gauss	G
gram	g
henry	H
hertz	Hz
hour	h
international unit	IU
joule	J
kelvin	K
kilogram	kg
liter, litre	l or L
meter, metre	m
minute	min
molar	*M*
mole	mol
newton	N
normal (concentration)	N
ohm	Ω
osmol	osmol
pascal	Pa
revolutions per minute	rpm
second	s
square centimeter	cm^2
volt	V
watt	W
week	wk
year	yr

Combining Prefixes

tera-	(10^{12})	T
giga-	(10^{9})	G
mega-	(10^{6})	M
kilo-	(10^{3})	k
hecto-	(10^{2})	h
deca-	(10^{1})	da
deci-	(10^{-1})	d
centi-	(10^{-2})	c

milli-	(10^{-3})	m
micro-	(10^{-6})	μ
nano-	(10^{-9})	n
pico-	(10^{-12})	p
femto-	(10^{-15})	f
atto-	(10^{-18})	a

Statistical Terms

correlation coefficient	r
degrees of freedom	df
mean	$\bar{x}$
not significant	NS
number of observations	n
probability	p
standard deviation	SD
standard error of the mean	SEM
"Student's" t test	*t* test
variance ratio	F

Others

adenosinediphosphatase	ADPase
adenosine 5′-diphosphate (adenosine diphosphate)	ADP
adenosine 5′-monophosphate (adenosine monophosphate, adenylic acid)	AMP
adenosine triphosphatase	ATPase
adenosine 5′-triphosphate (adenosine triphosphate)	ATP
adrenocorticotropic hormone (adrenocorticotropin)	ACTH
bacille Calmette-Guérin	BCG
basal metabolic rate	BMR
body temperature, pressure, and saturated	BTPS
central nervous system	CNS
coenzyme A	coA
deoxyribonucleic acid (deoxyribonucleate)	DNA
dihydroxyphenethylamine	dopamine
electrocardiogram	ECG
electroencephalogram	EEG
enteric cytopathogenic human orphan (virus)	ECHO
ethyl	Et
ethylenediaminetetraacetate	EDTA
gas-liquid chromatography	GLC
guanosine 5′-monophosphate (guanosine monophosphate, guanylic acid)	GMP
hemoglobin	Hb
logarithm (to base 10; common logarithm)	log
logarithm, natural	ln
methyl	Me
Michaelis constant	K_m
negative logarithm of hydrogen ion activity	pH
partial pressure of CO_2	P_{CO_2}
partial pressure of O_2	P_{O_2}
per	/
percent	%
radiation (ionizing, absorbed dose)	rad
respiratory quotient	RQ
specific gravity	sp gr
standard atmosphere	atm
standard temperature and pressure	STP
ultraviolet	uv
volume	vol
volume ratio (volume per volume)	vol/vol
weight	wt
weight per volume	wt/vol
weight ratio (weight per weight)	wt/wt

ABBREVIATIONS OF NAMES OF FREQUENTLY CITED JOURNALS

Acta Medica Scandinavica	Acta Med Scand
American Family Physician	Am Fam Physician
American Heart Journal	Am Heart J
American Journal of Cardiology	Am J Cardiol
American Journal of Clinical Nutrition	Am J Clin Nutr
American Journal of Clinical Pathology	Am J Clin Pathol
American Journal of Digestive Diseases	Am J Dig Dis
American Journal of Diseases of Children	Am J Dis Child
American Journal of Human Genetics	Am J Hum Genet
American Journal of the Medical Sciences	Am J Med Sci
American Journal of Medicine	Am J Med
American Journal of Obstetrics and Gynecology	Am J Obstet Gynecol
American Journal of Ophthalmology	Am J Ophthalmol
American Journal of Pathology	Am J Pathol
American Journal of Physical Medicine	Am J Phys Med
American Journal of Physiology	Am J Physiol
American Journal of Psychiatry	Am J Psychiatry
American Journal of Public Health	Am J Public Health
American Journal of Roentgenology	AJR
American Journal of Surgery	Am J Surg
American Journal of Tropical Medicine and Hygiene	Am J Trop Med Hyg
American Review of Respiratory Disease	Am Rev Respir Dis
Anaesthesia	Anaesthesia
Anesthesiology	Anesthesiology
Annals of Allergy	Ann Allergy
Annals of Internal Medicine	Ann Intern Med
Annals of Otology, Rhinology and Laryngology	Ann Otol Rhinol Laryngol
Annals of Surgery	Ann Surg
Annals of Thoracic Surgery	Ann Thorac Surg
Archives of Dermatology	Arch Dermatol
Archives of Environmental Health	Arch Environ Health
Archives of General Psychiatry	Arch Gen Psychiatry
Archives of Internal Medicine	Arch Intern Med
Archives of Neurology	Arch Neurol
Archives of Ophthalmology	Arch Ophthalmol
Archives of Otolaryngology	Arch Otolaryngol
Archives of Pathology and Laboratory Medicine	Arch Pathol Lab Med
Archives of Physical Medicine and Rehabilitation	Arch Phys Med Rehabil
Archives of Surgery	Arch Surg
Arthritis and Rheumatism	Arthritis Rheum
Blood; Journal of Hematology	Blood
Brain; Journal of Neurology	Brain
British Heart Journal	Br Heart J
British Journal of Obstetrics and Gynaecology	Br J Obstet Gynaecol
British Journal of Radiology	Br J Radiol
British Journal of Surgery	Br J Surg
British Medical Journal	Br Med J
Canadian Journal of Public Health	Can J Public Health
Canadian Medical Association Journal	Can Med Assoc J
Cancer	Cancer
Chest	Chest
Circulation; Journal of the American Heart Association	Circulation
Circulation Research	Circ Res
Clinical Pediatrics	Clin Pediatr (Phila)
Clinical Pharmacology and Therapeutics	Clin Pharmacol Ther
Clinical Science and Molecular Medicine	Clin Sci Mol Med
Clinical Toxicology	Clin Toxicol
Diabetes	Diabetes
DM, Disease-a-Month	DM
Endocrinology	Endocrinology
Gastroenterology	Gastroenterology
Geriatrics	Geriatrics
Gut	Gut
Human Pathology	Hum Pathol
Investigative Radiology	Invest Radiol
JAMA; Journal of the American Medical Association	JAMA
Journal of Allergy and Clinical Immunology	J Allergy Clin Immunol
Journal of Applied Physiology	J Appl Physiol
Journal of Biological Chemistry	J Biol Chem
Journal of Bone and Joint Surgery; American Volume	J Bone Joint Surg [Am]
Journal of Bone and Joint Surgery; British Volume	J Bone Joint Surg [Br]
Journal of Clinical Endocrinology and Metabolism	J Clin Endocrinol Metab
Journal of Clinical Investigation	J Clin Invest
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Journal of Thoracic and Cardiovascular Surgery	J Thorac Cardiovasc Surg
Journal of Trauma	J Trauma
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Lancet	Lancet
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Medicine (Baltimore)	Medicine (Baltimore)
New England Journal of Medicine	N Engl J Med

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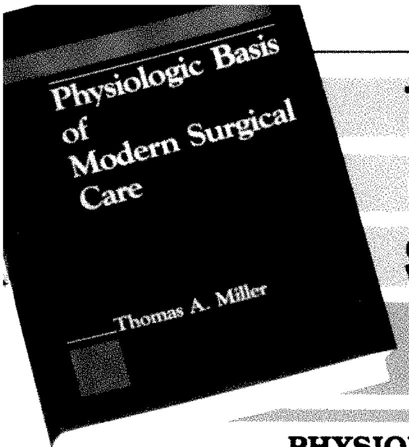

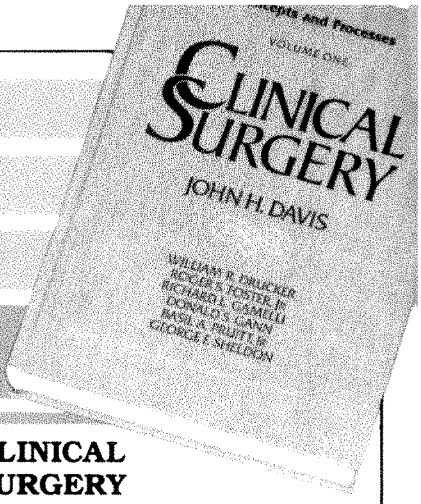

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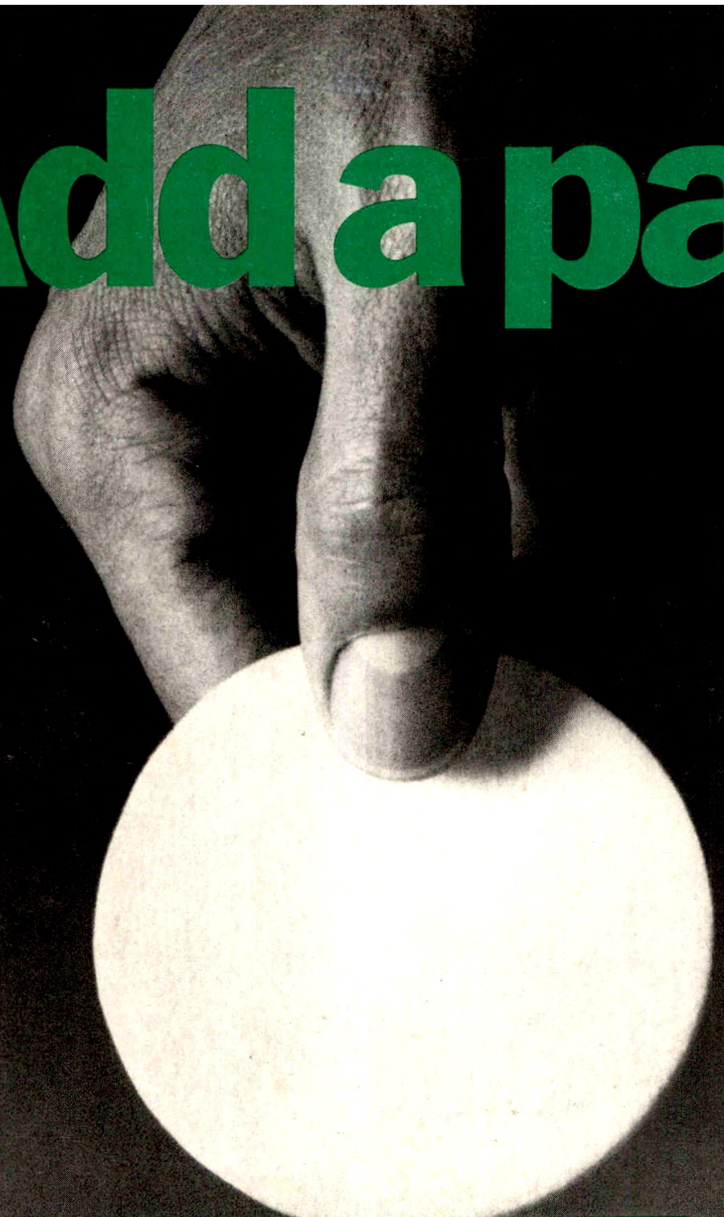

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BRIEF SUMMARY

INDICATIONS AND USAGE

TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary tract infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris*, *Providencia rettgeri*, and *Morganella morganii*).

Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.

Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.

Gynecologic infections caused by *Staphylococcus aureus*† (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus* species (excluding enterococci), *E coli*, *Proteus mirabilis*, *Neisseria gonorrhoeae*, *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*), *Fusobacterium* species,† and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species†).

Intra-abdominal infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*†), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*).

Bone and joint infections caused by *Staphylococcus aureus*.†

***NOTE:** Some strains of *Staphylococcus epidermidis* are resistant to cefotetan.

†Efficacy for this organism in this organ system was studied in fewer than ten infections.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.

PRECAUTIONS

GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state. Prothrombin times should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels of Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approx 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approx 2-4 times the usual human dose), only 1 of 10 treated animals was affected, and the degree of degeneration was mild. Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In clinical studies the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5 percent of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4 percent of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2 percent of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2 percent of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than one percent of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

DOSAGE AND ADMINISTRATION

TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dose*	Every 12 hours
10-30	Usual Recommended Dose*	Every 24 hours
<10	Usual Recommended Dose*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED

CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

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Annals of Surgery
Department of Surgery
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Recurrent Hepatic Hemangiomas

Possible Association with Estrogen Therapy

ROBERT L. CONTER, M.D. and WILLIAM P. LONGMIRE, JR., M.D., F.A.C.S.

Hemangiomas are the most common benign tumors occurring in the liver. However, the natural history of hepatic hemangiomas has not been well defined. Four patients (3 women, 1 man) with recurrent giant liver hemangiomas underwent either surgical or radiation therapy as initial treatment for the primary tumor. The average time until recurrence was 14 years, and each tumor weighed more than 600 g. Each of the female patients had been given chronic estrogen (Premarin) replacement therapy. Three of the four patients underwent surgical resection for intractable symptoms or progressive enlargement. It is believed that estrogen replacement therapy may play a role in the pathogenesis of these tumors. Furthermore, operative intervention should be considered in patients with recurrent giant liver hemangioma.

HEMANGIOMAS ARE THE MOST COMMON benign tumors occurring in the liver.[1] Small hemangiomas of the liver are generally asymptomatic. However, giant hemangiomas, those larger than 4 cm, frequently present as an abdominal mass associated with vague symptoms of upper abdominal pain and fullness. Since a risk of fatal spontaneous hemorrhage from these hemangiomas exists,[2] the majority of surgeons believe that symptomatic giant hemangiomas of the liver require surgical intervention.

From the Department of Surgery, UCLA Hospital and Clinics, Los Angeles, California

The natural history of hepatic hemangioma has not been well defined. Factors that allow some lesions to remain dormant or regress and others to undergo rapid growth are poorly understood. Four patients who had previously received either surgical or radiation therapy for large symptomatic liver hemagiomas have recently been managed at UCLA. Each of these patients returned with similar clinical findings and were found to have recurrent hepatic hemangiomas. Their individual case reports follow and form the basis for this paper (Table 1).

Case Reports

Case 1

A 59-year-old woman presented with epigastric and right-sided abdominal pain and bloating. Thirteen years prior to her admission she was diagnosed as having a large hepatic hemangioma and underwent 5 months of cobalt radiation therapy. Follow-up liver-spleen scan showed that the liver mass had receded, and her symptoms disappeared. She returned 13 years later with upper abdominal symptoms, and subsequent angiogram revealed evidence of a recurrent hemangioma (Fig. 1). Her past history was remarkable considering her total hysterectomy at age 39 and Premarin hormone replacement for 20 years. She underwent a right hepatectomy for removal of a recurrent

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TABLE 1. *Clinical Summary of Patients with Recurrent Giant Hemangiomas*

Patient No.	Initial Treatment	Time to Recurrence (yr)	Tumor Size (g)	Estrogen Therapy	Treatment of Recurrence
1	Radiation	13	950	Premarin	Surgery
2	Radiation	16	810	None	Surgery
3	Surgery	17	650	Premarin	Observation
4	Surgery	11	690	Premarin	Surgery

hemangioma weighing 950 g. In addition, a smaller hemangioma was removed from the left lateral segment. Pathologic diagnosis of both specimens revealed cavernous hemangioma. During the ensuing 8 years she has been well and without further abdominal symptoms or change in her liver scan.

Case 2

A 49-year-old male physician was diagnosed with a hemangioma involving the entire left lobe of the liver during laparotomy for cholecystitis. He was subsequently treated with postoperative radiation (dose unknown) and remained symptom-free for 16 years until he was admitted to UCLA with recurrent attacks of fever, chills, upper abdominal pain, and transitory jaundice. A firm 15-cm mass was palpable to the left of the xiphoid and a large filling defect was demonstrated in the left lobe of the liver. At laparotomy, following a negative common bile duct exploration, a left hepatic lobectomy removed an 810-g mass (Fig. 2). Pathologic diagnosis revealed multiple capillary and cavernous hemangiomas with areas of extensive scarring and necrosis. A bile duct was identified entering the tumor mass. It was assumed that pieces of necrotic tissue embolized into the biliary systems causing his intermittent attacks of fever and jaundice. He was well for 3 years following resection until he was found to have hemangiopericytoma in the left chest, unrelated to the hepatic hemangioma. This patient was also found to have a melanoma near the left scapula treated by excision and systemic chemotherapy (thiotepa) at age 48.

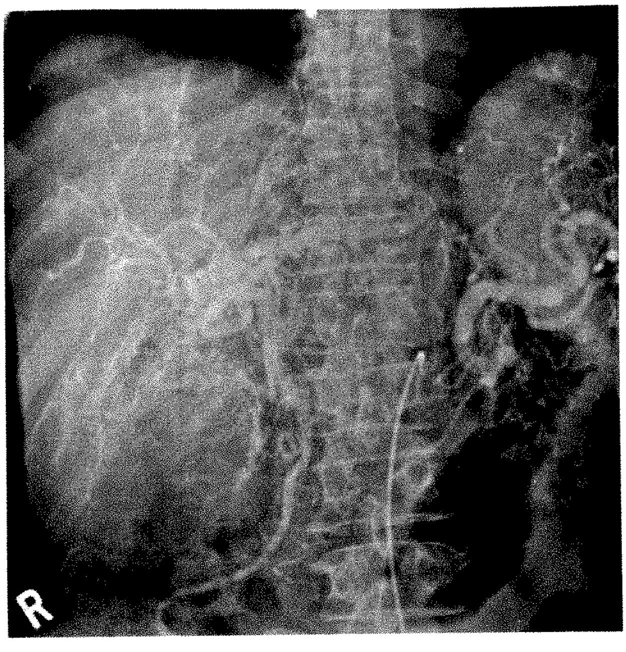


FIG. 1. Angiogram of a recurrent cavernous hemangioma; note downward and medial displacement of gastroduodenal artery from a giant hemangioma of the right lobe of the liver.

Case 3

A 57-year-old woman was referred to UCLA in 1969 after a laparotomy revealed a large cystic mass in the left lobe of the liver. She had presented with symptoms of abdominal pain, early satiety, weight loss, and a mass in the left upper quadrant. Her past history was remarkable considering that she had an appendectomy and total hysterectomy at age 37 with chronic estrogen replacement therapy. An arteriogram demonstrated a large mass in the lateral segment of the left lobe of the liver. A left lateral segmentectomy was performed for a 900-g cavernous hemangioma (Fig. 3). A few small punctate hemangiomas were seen in the medial segment of the left lobe. She has been asymptomatic for 17 years. However, during the course of a recent evaluation for an unrelated gynecologic condition, a CT scan revealed a 7-cm mass in the remaining left lobe consistent with cavernous hemangioma. She has stopped taking premarin and has been advised to have routine follow-up scans and observation. Surgery is considered unwarranted for this recurrent asymptomatic hemangioma in this 74-year-old patient.

Case 4

A 55-year-old woman presented to UCLA with complaints of an enlarging abdomen with right-sided abdominal pain, nausea, and vomiting. These symptoms had gradually increased in intensity over a period of 17 years finally becoming severe enough to cause the patient to seek medical attention. Evaluation revealed a large mass in the right lobe of the liver. A 650-g cavernous hemangioma was removed via an extended right hepatectomy; however, it was not possible to completely excise the lesion since it surrounded both right and left hepatic veins. She remained in good health for 11 years until similar symptoms recurred and she again sought relief. A hepatic angiogram demonstrated an extensive vascular lesion (Fig. 4). Understanding that it would be impossible to completely excise this lesion, the patient underwent a partial hepatic resection for a recurrent cavernous hemangioma (690 g). She remains asymptomatic without enlargement on CT scan 1 year following resection. It is interesting to note that this patient was taking Premarin for over 15 years, 5 years prior to her first hepatectomy.

Discussion

To the best of our knowledge, this paper represents the first report of recurrent hepatic hemangiomas following ablative treatment. Growth of the tumor was quite slow, and surgical resection was performed for intractable symptoms or progressive enlargement. Three of the four recurrences developed in patients receiving estrogen therapy. This pattern of recurrence may repre-

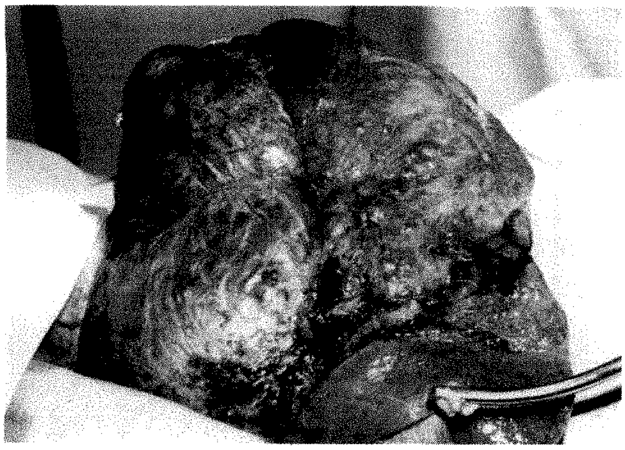


FIG. 2. Operative photograph of a recurrent giant hemangioma of the medial segment of the left lobe of the liver; the clamp points to the grossly normal left lateral segment.

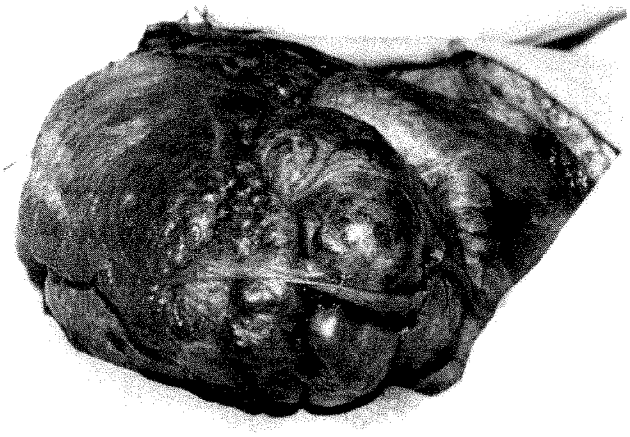


FIG. 3. Photograph taken at laparotomy for recurrent hemangioma of the lateral segment of the left lobe of the liver.

sent a new manifestation in the natural history of this disease.

Hemangiomas are the most common benign tumors of the liver. The first report of a liver hemangioma was by Frerichs[3] in 1861. Adami[4] described 20 cases (1.4%) of cavernous hemangioma in 1400 autopsies, while Ochsner and Halpert[5] reported a 2.3% incidence of hepatic hemangioma a half century later. Hemangiomas are most frequently encountered in patients in the third through fifth decades of life, but can occur in any age group. The average age of patients presenting with symptomatic lesions is approximately 45 years.[6] The disease is found most often in females with several series reporting a 4:1 or 5:1 ratio.[7,8] The vast majority of patients are asymptomatic, and most tumors are less than 4 cm in diameter. Multiple hemangiomas, however, have been reported in 9–22% of patients.[5,9] The mean age of our patients (three women, one man) when first diagnosed with a hemangioma was 50.7 years, although symptoms had been present for prolonged periods in each patient prior to diagnosis. Recurrence of hepatic hemangioma was slow and progressive, averaging slightly more than 14 years before upper abdominal symptoms forced these patients to seek medical attention.

Hepatic hemangiomas appear grossly as nodules embedded in the liver substance, red, blue, or gray, depending on the amount of fibrosis; they have a sponge-like structure on sectioning. Histologically, they are composed of large endothelium-lined vascular spaces separated by fibrous septa of varying thickness. Trastek et al.[10] have suggested that enlargement of liver hemangioma was due to ectasia rather than by a new progressive growth of tissue. The recurrent hemangioma in our patients weighed more than 600 g and demonstrated a classic histologic pattern (Fig. 5). Such recurrences could hardly be considered due to mere expansion, dilatation, or distension of preexisting tissue. It would seem that the proper interpretation of the pathologic process is that the extensive recurrence of these hemangiomas is the result of growth of new cellular tissue.

The etiology of hemangiomas of the liver is purely speculative. The vast differences in clinical course that exist between children and adults and the findings of spontaneous regression, growth,[10] and rupture[2] reflect a wide variability in the natural history of this disease.

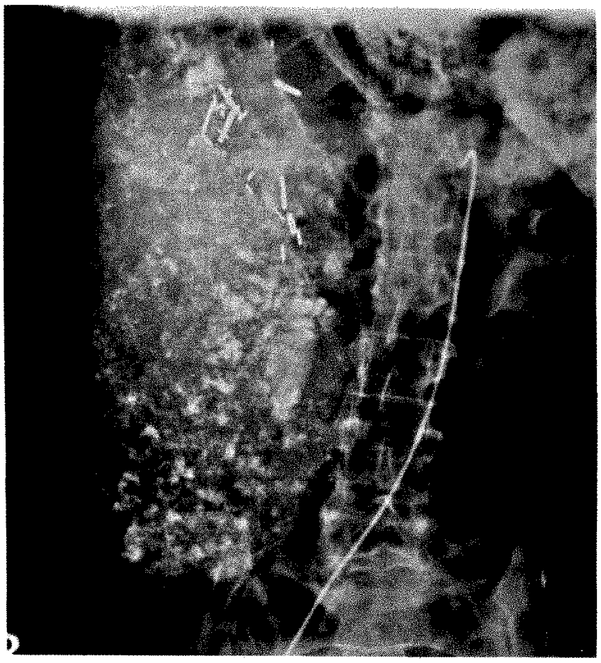
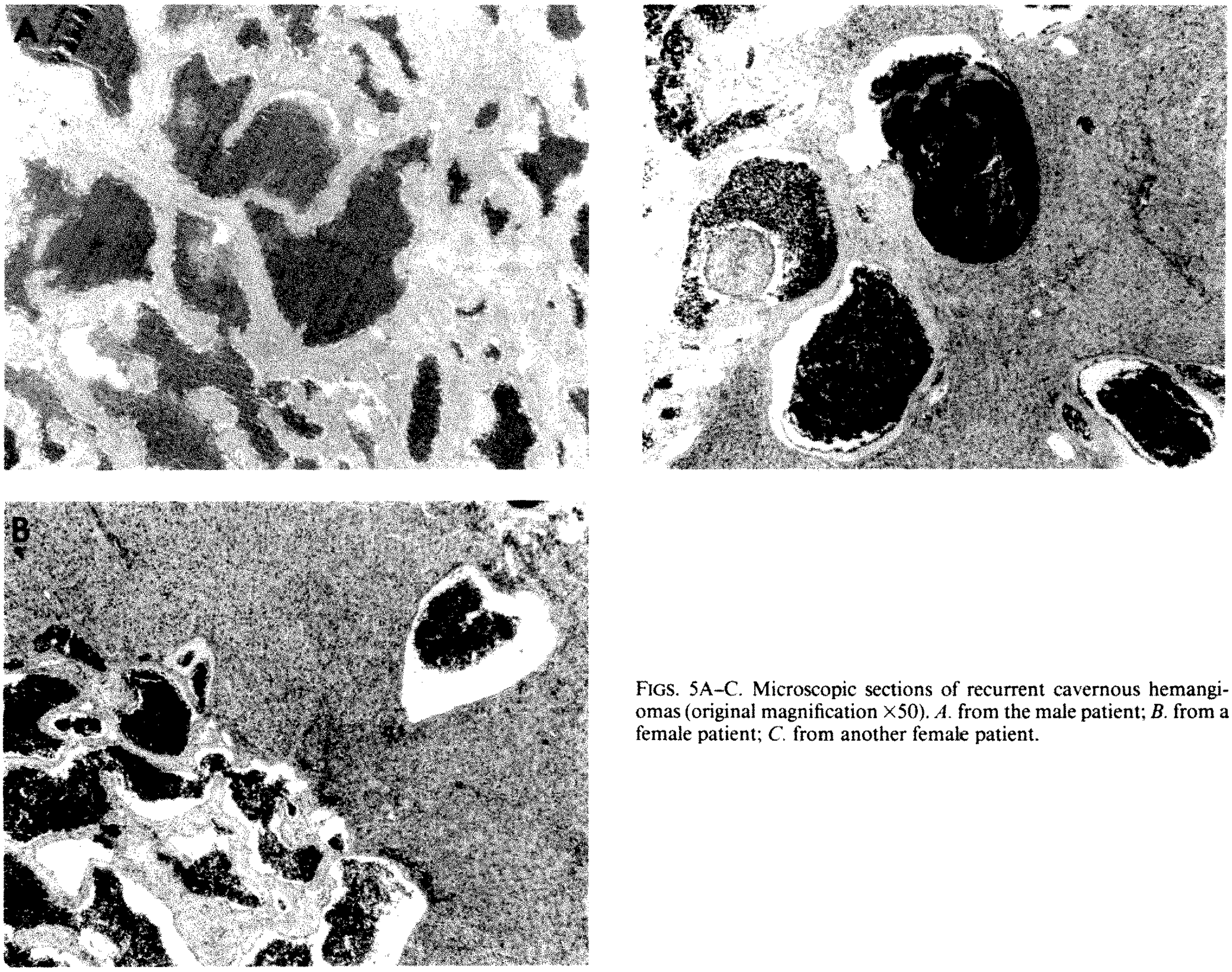


FIG. 4. Angiogram of a giant recurrent hemangioma of the right lobe of the liver.



FIGS. 5A–C. Microscopic sections of recurrent cavernous hemangiomas (original magnification ×50). *A.* from the male patient; *B.* from a female patient; *C.* from another female patient.

Several authors suggest that these vascular lesions are benign congenital hamartomas that grow slowly from birth.[5,11] Moore[11] considers hemangiomas to be acquired tumors resulting from areas of focal hepatic necrosis and subsequent regeneration. Robbins[12] suggests that these lesions may be true neoplasms occurring spontaneously and therefore consist of new blood vessels and tissue rather than dilatations of previous telangiectatic lesions.

Baum et al.[13] first called attention to the possible relationship between the use of oral contraceptives and the subsequent development of hepatic tumors. Since that time the literature has reflected numerous reports of the diagnosis of benign tumors such as hepatic adenoma,[14] focal nodular hyperplasia,[15] or hamartomas[16] in women receiving estrogen replacement therapy. Subsequent reports, however, have also documented malignant hepatic tumors in women receiving oral contraceptive steroids.[17,18] Furthermore, it has been suggested that oral contraceptives may affect normal hepatic tissue by inducing hepatomegaly and periportal congestion.[19] The scope of these observations suggests that oral contraceptive steroids may also play a role in the pathogenesis of vascular tumors of the liver.

Klatskin[20] reviewed more than 400 patients with benign liver tumors (hepatic adenomas and focal nodular hyperplasia) and found them to be larger and more prone to hemorrhage and rupture in women receiving oral steroid replacement. He attributed these events to vascular changes and was able to demonstrate a spectrum of findings from minute areas of hemorrhage to multiple, small, diffuse liver hemangiomas. These diffuse hemangiomas (peliosis hepatis) have also been reported in patients given anabolic steroids.[21,22] In addition, Morley et al.[23] have reported rapid growth of a hepatic hemangioma associated with exogenous estrogen administration. Three of the four recurrent hepatic hemangiomas in our series occurred in women who had been receiving oral estrogen therapy prior to their original surgery, and who continued with estrogen replacement until their recurrence was diagnosed. Klatskin[20] and Mays et al.[24] have reported post resection recurrence of hepatic adenoma and focal nodular hyperplasia in patients who continued to use oral contraceptives. The exact role of estrogens in the pathogenesis and natural history of primary or recurrent hepatic hemangiomas is unclear. However, one may speculate that the relationship between estrogens and angiomatous lesions of the skin and gingiva may also exist within the hepatic parenchyma.

These cases of recurrent hepatic hemangioma demonstrate several important features of this disease: (1) the possible association between estrogen replacement therapy and the development of these tumors; (2) the very slow growth pattern of these tumors, measured in decades rather than years; (3) the recurrence of these hemangiomas by growth of new cellular tissue, not by ectasia; (4) has been the effectiveness of radiation therapy in reducing the size of the tumor but not in curing the disease; and (5) the fact that reoperation may be required for recurrent symptoms.

Summary

We have recently treated four patients with recurrent giant hemangioma of the liver. There were three women and one man with an average age on presentation of 50.7 years. Each of the women had been receiving oral estrogen replacement therapy for a minimum of 15 years. Two of the patients (one man, one woman) had received prior radiation therapy as initial treatment. Symptoms of upper abdominal discomfort and pain, nausea, vomiting, and a palpable mass were common on presentation. Three of the four patients underwent surgical resection of giant hepatic hemangioma.

The natural history of primary or recurrent hepatic hemangiomas remains poorly defined. We believe that estrogen replacement therapy may play a role in the pathogenesis of these tumors. Furthermore, operative intervention should be strongly considered in patients who present with recurrent giant liver hemangiomas.

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Major Liver Resection for Hilar Cholangiocarcinoma

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Between 1968 and 1984 liver resection with curative attempt was performed in 22 patients with hilar cholangiocarcinoma. Right lobectomy was performed in 4 patients, extended right lobectomy in 7, left lobectomy in 8, and excision of the median segment segment of the left lobe (segment IV) in 3. Bilio-enteric continuity was restored by hepatocholedochostomy in 17 patients and hepatojejunostomy in 4. (One patient had external transhepatic catheter drainage and no internal bile drainage.) Operative mortality rate was 27% and caused by excessive intraoperative bleeding, sepsis, or liver insufficiency. Postoperative complications occurred in 57% of patients surviving the operation and were due mainly to leakage from the hepatocholedochostomy. Median survival was 6 months, and one third of the patients survived 1 year. Three patients survived 10 years and were among the four patients in whom a tumor-free resection margin was obtained (one of them died in the postoperative phase). It is concluded that resection of hilar cholangiocarcinoma may give long-term survival if a free resection margin is obtained. The importance of a free resection margin indicates that surgery should be aggressive and include liver resection.

RESECTION IS THE ONLY TREATMENT that offers a hope for cure of bile duct cancers. However, operative morbidity and mortality rates have been high, and long-term survival has been exceptional. This is true especially for hilar cholangiocarcinoma described by Altemeier et al.[1] in 1957 and by Klatskin[2] in 1965. Although this tumor is rare, it should be recognized that it has an annual incidence of about 1300 in the United States.

In his review of the literature in 1983, Boerma collected a total of 75 cases of local resection of hilar cholangiocarcinoma.[3] Operative mortality rate was 11%. Mean survival was 19 months, and there was no 5-year survivor. Local recurrence was the usual cause of death. It may therefore be assumed that curative resection should include resection of adjacent parts of the liver.

The first one-center series of liver resection for hilar cholangiocarcinoma that comprised more than ten patients came from our group in 1980[4] and was soon followed by four other reports. Tsuzuki et al.[5] reported 15 cases with a 50% actuarial survival of 24 months and a longest survival of 3 years and 8 months. Blumgart et al.[6] reported 12 liver resections with a mean survival of 17 months; seven of their patients were alive at the time of the report. Langer et al.[7] performed 12 resections of high bile duct tumors, and all or most of them included liver resection. They reported a mean survival of 28 months and two 5-year survivors who later died of recurrent disease. In a series by Mizumoto et al.[8] 13 hepatic resections were followed by a mean survival of 12 months: the longest survival was almost 6 years in a patient having undergone right lobectomy.

The present paper summarizes our experience from 22 consecutive liver resections for hilar cholangiocarcinoma during a 16-year period.

Materials and Methods

Patients

Twenty-two patients with hilar cholangiocarcinoma underwent a combined bile duct and liver resection between 1968 and 1984 (Fig. 1). There were 13 men and 9 women with a median age of 56 years (range: 33–68 yr). Fifteen patients were referred from other hospitals; one patient had undergone cholecystectomy 30 years earlier.

All patients were jaundiced at operation, but none had been jaundiced for more than 2 weeks before diagnostic procedures were started. Common complaints were pain (64%), loss of appetite (59%), weight loss

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No reprints available.

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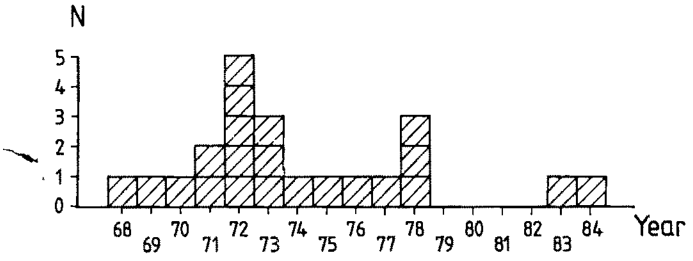

FIG. 1. Number of patients who underwent attempted curative resection between 1968 and 1984.

TABLE 1. *Diagnostic Procedures*

	N	Positive Finding N (%)
PTC	13	13 (100)
Exploratory laparotomy	9	8 (89)
Angiography	19	11 (58)
Percutaneous fine needle biopsy	9	7 (78)
Ultrasound	3	2 (67)
CT	3	1 (33)

(50%), and fatigue (41%). Six patients had experienced minor symptoms from the upper right quadrant for many years.

Preoperative Investigations and Management

The results of various diagnostic procedures are summarized in Table 1. Percutaneous transhepatic cholangiography (PTC) was used in 13 patients. The catheter was left for bile drainage in 11 cases but failed in 3, in whom bile leakage, cholangitis, or suspicion of visceral perforation led to emergency laparotomy and replacement with T tube drainage.

Exploratory laparotomy was the initial diagnostic procedure in nine patients. It was performed only once after 1979 when diagnostic procedures such as ultrasonography, computed tomography (CT), and endoscopic retrograde cholangiopancreaticography (ERCP) were available. Surgical exploration ended in T tube drainage in four patients and a radical procedure in one, whereas three patients underwent a subsequent PTC. Seven of the exploratory laparotomies were performed at other hospitals before referral to us.

Arteriography was performed in all but the first three patients. It was used to assess resectability by identifying major involvement of the hepatic artery and the portal vein, or involvement of both the right and left branches of the portal vein. Angiography was valuable for planning the resection in 11 patients; in the remaining eight no abnormalities were seen.

Percutaneous fine needle aspiration biopsy, guided by PTC or angiography, was performed in nine patients. A positive diagnosis of cancer was obtained in seven patients.

Tumors were considered unresectable when they encased the proper hepatic artery, the main trunk of the portal vein, both the right and left branches of the portal vein, or when they extended beyond the second bile duct confluence bilaterally.

The bile ducts were drained before resection in 15 (68%) patients for a period of 24 days (median) (range: 11–76 days). Eight patients had percutaneous transhepatic drainage, and seven patients were drained through a tube inserted during surgery.

Pathology

The size of the primary lesion varied between 2 and 5 cm. The distal extension of the tumor included the cystic duct in five patients but was otherwise restricted to the main hepatic duct.

In order to describe the antomic location and the pattern of growth of the tumors, we have modified the classification of Bismuth and Corlette.[9] Since it appears that tumors that extend into the right or left duct may be

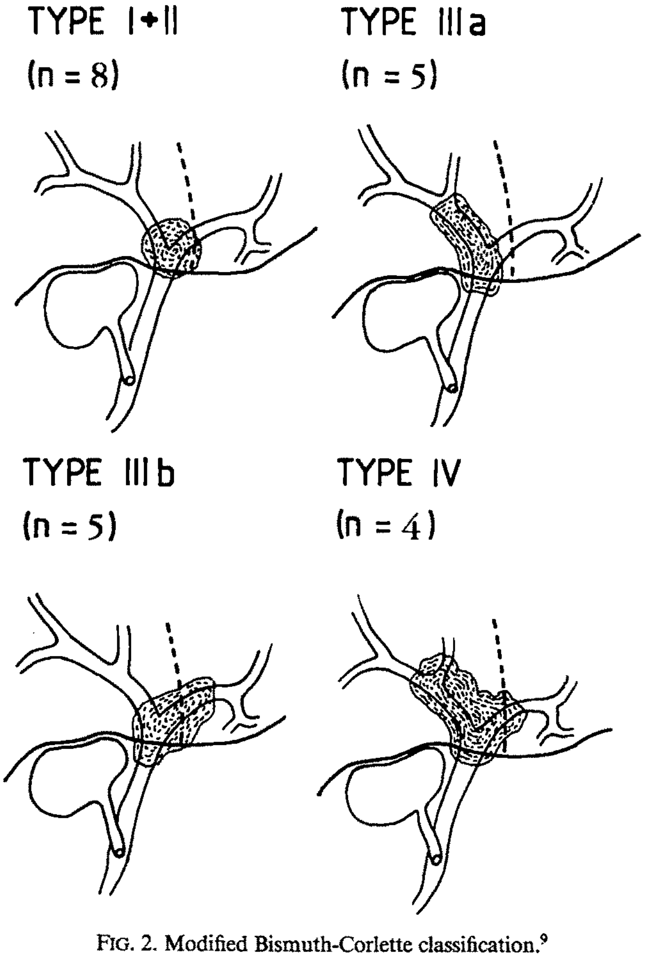

FIG. 2. Modified Bismuth-Corlette classification.[9]

TABLE 2. *Surgical Procedures*

	Procedure	N
Type I + II (N = 8)	Left lobectomy + hepatocholedochostomy	3
	Right lobectomy + hepatocholedochostomy	2
	Resection of segment IV + hepatocholedochostomy	3
Type IIIa (N = 5)	Right lobectomy + hepatocholedochostomy	1
	Right lobectomy + hepatojejunostomy	1
	Extended right lobectomy + hepatocholedochostomy	3
Type IIIb (N = 5)	Left lobectomy + hepatocholedochostomy	2
	Left lobectomy + hepatohepaticostomy	1
	Left lobectomy + hepatojejunostomy	1
	Left lobectomy + Lig RHD + transhepatic drainage	1
Type IV (N = 4)	Extended right lobectomy + hepatocholedochostomy	2
	Extended right lobectomy + hepatojejunostomy	2

Lig RHD = ligation of the right hepatic duct.

treated differently because of the different anatomy, we have subdivided type III into two types (Fig. 2): type IIIa, extension into the right but not the left duct; and type IIIb, extension into the left but not the right duct. Type IV denotes tumor growth into both the right and the left hepatic ducts. Eight tumors were located at the hilum with minor extensions into the hepatic ducts (type I + II). Extension along the right (type IIIa) or the left (type IIIb) hepatic duct dominated in five cases each. Tumor growth along both hepatic ducts (type IV) was seen in four cases (Fig. 2).

Six patients had tumor growth into the adjacent liver parenchyma, and another six had unilateral liver metastases. Regional lymph node metastases were present in four patients.

Microscopic examination of the resection margin demonstrated no evidence of disease in 4 (18%) patients, equivocal findings in 5 (23%), and tumor growth in 13 (59%).

Surgical Procedures

The surgical procedures are summarized in Table 2. A midline incision was used during the first half of the study period but was later replaced by a right-sided transrectal approach. Thoracotomy was performed in two patients. All lymph nodes in the hepatoduodenal ligament, around the coeliac axis, and at the liver hilum were removed for microscopic examination. Inflow vessels in the liver hilum were ligated before resection of the liver in half of the patients.

Patients with a type I + II tumor underwent left or right lobectomies or resection of the median segment of the left lobe (segment IV). Left lobectomy was performed in all patients with a type IIIb tumor. Type IIIa and IV tumors were removed with simple or extended right lobectomies. Cholecystectomy was performed in all patients.

Reconstruction was done as an end-to-end biliary-biliary anastomosis (N = 17) or as an end-to-side biliary-enteric anastomosis on a Roux-en-Y loop (N = 4). Reconstruction was considered technically impossible in one patient who was managed postoperatively with percutaneous transhepatic drainage alone. Preoperatively placed PTC catheters were left for drainage after surgery. Patients without preoperative bile drainage received a T tube or a transhepatic drainage catheter during the operation. No patient received chemotherapy or radiotherapy.

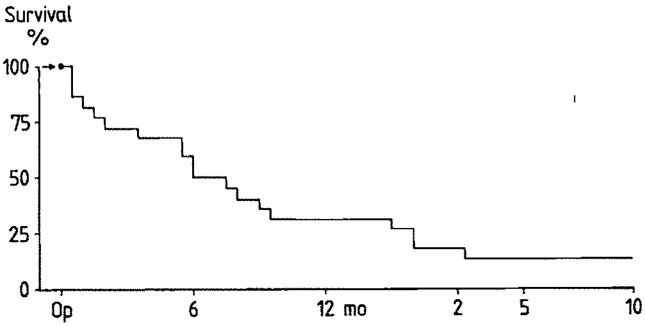

FIG. 3. Survival rates.

Results

Survival (Fig. 3)

The overall median survival was 7 months (range: 0–170 months). Excluding operative deaths (N = 6), survival was 9 months (median) (range: 4–170 months).

Seven (32%) patients lived for more than a year. Four of them survived 1.5 to 2.5 years. The remaining three patients lived for more than ten years after resection; 2 of them were alive after 10 and 11.2 years, respectively, while the third patient died of recurrent disease after 14.3 years. Except for deaths caused by surgery, all deaths were due to recurrent disease.

A resection margin free of tumor had a major impact on survival. The three patients surviving for more than 10 years had a resection margin free of disease, whereas none of the others had (except for one patient who died from the operation). Two of the three 10-year survivors had involvement of adjacent liver parenchyma, and two of the patients surviving more than 1 year had ipsilateral liver metastases. The presence of liver metastases, growth into the liver parenchyma, or the type of operation did not vary with prognosis. Spread to lymph nodes in the hepatoduodenal ligament was always accompanied with a poor survival (less than 1 year).

Recurrence

Fourteen patients died of recurrent disease, situated in the liver hilum or the liver parenchyma in all but one. The time for detection of local recurrence varied from 2 months to 9 years (median: 5 months). Liver metastases were demonstrated in two patients, after 2 months and 13 years, respectively. Peritoneal secondaries were found in five patients and bone metastases in two patients.

Nine patients underwent reoperation because of recurrence: atypical liver resection (1), resection of a large extrahepatic tumor (1), biliogastric anastomosis (1), hepatojejunostomy (1), placement of an internal splint (3), T tube placement (1), and exploratory laparotomy (1). Two of the reoperated patients died during the postoperative hospitalization. Five patients with recurrent biliary obstruction did not undergo reoperation but received a percutaneous transhepatic catheter for drainage of bile.

The presence or absence of abnormal vessels at angiography did not help in predicting whether or not the resection was microscopically radical; resection was microscopically radical in 2 of 11 patients with abnormal findings and in 2 of 8 patients with no abnormalities.

Complications

Six patients died from the operation, an operative mortality rate of 27%. The main causes of death were intraoperative bleeding, liver necrosis, and infection (Table 3). There was no change in operative mortality rate during the study period.

Major complications occurred in 9 (56%) of the 16 patients who survived the operation (Table 4). Most of them were related to leakage from the hepatocholedochal or hepatojejunal anastomosis. Liver insufficiency developed in a patient who underwent an 85% hepatectomy. Following right lobectomy, the remnant liver rotated in one patient and caused occlusion of the hepatojejunostomy. The patient receiving a transhepatic catheter for drainage of bile (and no biliodigestive shunt) had several episodes of cholangitis.

TABLE 3. *Operative Mortality Rates*

Cause of Death	Length of Survival (d)
Intraoperative bleeding and coronary infarction	2
Intraoperative bleeding and multiple organ failure	3
Liver necrosis and failure	12
Leaking hepatocholedochostomy	27
Liver necrosis and failure	42
Subphrenic abscess and bleeding duodenal ulcer	47

Four patients had no preoperative drainage of bile. Two of them died from major intraoperative bleeding whereas the other two had an uneventful postoperative course.

Discussion

Bile duct tumors should be regarded more as regional than local. Since bile ducts have thin walls, a biliary tumor is apt to involve surrounding tissues. It spreads along the periductal lymphatic network, perineural lymph clefts, and periductal venules and arterioles and may infiltrate the bile duct wall submucosally over a wide distance.[10,11] Regional or hepatic metastases may be expected in 30–50% of the cases.[3] Distant metastases are otherwise quite infrequent, appear late, and are usually located in the lesser omentum and occasionally at other sites within or outside the abdominal cavity.

The first attempt at local resection seems to have been described by Brown and Myers in 1954.[12] However, before 1973 and the early work of Longmire et al.[13] at-

TABLE 4. *Operative Morbidity Rates*

	N	Type of Operation
Liver insufficiency + leaking hepatojejunostomy	1	ERL, jej
Leaking hepatojejunostomy	1	ERL, jej
Leaking hepatocholedochostomy and subphrenic abscess	2	LL, chol RL, chol
Occluded hepatojejunostomy	1	RL, jej
Subphrenic abscess	1	RL, chol
Cutaneous bile fistula	2	LL, chol LL, chol
Cholangitis	1	LL, PTD
Total	9 (56%)	

(E)RL = (extended) right lobectomy; LL = left lobectomy; jej = hepatojejunostomy; chol = hepatocholedochostomy; PTD = percutaneous transhepatic drain.

tempts at resection were exceptional and tumors discovered at laparotomy were only intubated, if possible. Most patients received no treatment and only limited diagnostic work-up. The pessimistic attitude was summarized by Blumgart et al.[6] caused by difficulties in the following: (1) preoperative diagnosis; (2) histologic confirmation; (3) excisional therapy; and (4) creation of a reliable bilio-enteric anastomosis. However, the situation has changed dramatically in recent years because of the availability of modern imaging methods and the improvements of surgical technique.

It has been repeatedly emphasized that tumor cells often remain after a macroscopically radical resection. Beazley et al.[14] were able to get free margins in 7 out of 16 resected cases, most of whom had undergone liver resection. One would expect the risk of residual cancer to be even greater after local resection alone. This view is substantiated in a report of Mizumoto et al.[8] in which a free margin was achieved in only 1 of 11 locally resected cases. Local recurrence has also been the main cause of death when resection of the quadrate lobe has been added to the local resection of the confluence, and no 5-year survivor has been reported.[3] Thus, resection of the bifurcation, alone or with quadrate lobe resection, is likely to leave cancer cells at the margin and to add little to the prospect of a good prognosis. Residual cancer increases the risk of early complications related to poor healing of the biliary-enteric anastomosis: leakage, abscess formation, sepsis.

Early reports indicated that high bile duct tumors are more common in the left, or the left part of the confluence, than in the right duct.[15] There is no support for such an opinion in the study of Weinbren and Mutum,[16] who found tumors on the right side in 21% and on the left side in 11% of their cases. As noted by Longmire et al.[13] the opinion of left side predominance probably reflected the fact that right-sided tumors were regarded as intrahepatic or untreatable. Most early attempts at liver resection were thus on the left side. However, the possibility of performing a radical resection and getting a reliable hepatojejunostomy is better when the tumor is situated on the right side. The right hepatic duct has a maximum length of 1 cm, which means that the tumor usually extends beyond the secondary confluence. The comparatively long left duct offers better possibilities for radical resection on the right side and has led to an increased number of right lobectomies. Most of our recent patients were operated with extended right lobectomies as were 9 (75%) of 12 cases of liver resection reported by Blumgart et al.[6] This approach is supported by the recent study of Mizumoto et al.[8] who demonstrated that about half of the patients have direct invasion of hepatic parenchyma at the hilum and that a similar number of patients have invasion of bile ducts draining the caudate lobe or direct invasion of caudate lobe parenchyma. It follows that the caudate lobe should be removed together with extrahepatic bile ducts and adjacent liver parenchyma. A tumor located at or close to the right hepatic duct should be resected with an extended right lobectomy to ensure complete removal of the caudate lobe and process. The chances of radically excising a tumor situated in the left duct are somewhat smaller because left lobectomy, or extended left lobectomy, does not ensure complete removal of the caudate process.

Most postoperative complications are related to leakage of the anastomosis between the hepatic ducts and the distal common bile duct or a jejunal loop. Like other authors,[5,6] we have abandoned biliary-biliary anastomosis in favor of hepatojejunostomy (on a 60-cm long Roux-en-Y loop) since it appears to carry a lower postoperative morbidity rate and increases the possibility of a radical resection.

Modern palliative measures include percutaneous, endoscopic, or surgical intubation and are accompanied by a 30-day mortality rate of roughly 30% and frequently by a poor quality of life.[6,7,17-19] Comparison with biliary-enteric bypass, with or without resection, is difficult because of differences in attitude and patient selection, but it is often noted that the quality of survival is good after surgery and appears better than after intubation alone.[6,7]

In summary, we believe that hilar cholangiocarcinoma in a patient fit for surgery should be carefully assessed with respect to a resection procedure, which in most cases should include liver resection. This attitude is based on the difficulty in obtaining a free resection margin if less radical procedures are used. It is also based on the potential for cure or long-term palliation with a good quality of survival and the fact of poor survival and quality of life with other surgical procedures or with intubational techniques.

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Blunt Trauma to the Liver

Analysis of Management and Mortality in 323 Consecutive Patients

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This study represents a 6 year 4 month experience with blunt trauma to the liver of patients from the Maryland Institute for Emergency Medical Services Systems, a major regional trauma center. The significance of this study is that it describes a large, relatively homogeneous population and analyzes what the state of the art for liver trauma has been in a center dedicated solely to trauma that has a full-time staff of trained traumatologists. Three hundred twenty-three consecutive patients with blunt liver trauma are presented, representing 3.5% of 9271 patients admitted to the institute over the period of this study. Ninety per cent had associated traumatic injuries requiring operative intervention. A mortality rate of 31% (101 patients) was noted; 41.5% of the deaths, due primarily to liver injury, occurred intraoperatively during the initial operation following admission. The use of simple suture techniques and resectional debridement to control hemorrhage are advocated. Anatomic lobectomy, intracaval shunting, and hepatic artery ligation were uniformly unsuccessful. The use of drains was associated with a significantly increased incidence of infectious complications ($p < 0.00002$).

> "Rupture of the liver is fortunately an accident not often met with but one which, when it is seen, may be associated with a condition of the patient as serious as anyone can meet in the surgical practice. While small lacerations of the liver substance may be, and no doubt are, recovered without surgical interference; if lacerations are extensive and vessels of any magnitude are torn hemorrhage will, owing to the structural arrangement of the liver, go on continuously and by the time such a patient comes under the care of a surgeon, the general state is almost invariably bound to be extremely grave from the hemorrhage alone or from hemorrhage and shock combined. This is perhaps especially the case in that class of injury due to *contusing* violence in which there is often gross injury inflicted on parts other than the liver and when shock is liable to be more severe than in localized injuries caused by sharp instruments" (J. Hogarth Pringle, 1908)[1]

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IN THE INTERVENING YEARS since Pringle's *notes* on hepatic trauma, the surgeon's frustration in managing serious "contusing" injury to the liver along with the mortality rate associated with it has remained virtually unchanged. Numerous large series dealing with the management of complex hepatic trauma have been reported. Most of these have come from large urban trauma centers treating a large percentage of penetrating injuries. Often the liver injury is an isolated one, and associated extra-abdominal injuries are not present. In contrast, this study represents the experience gained over a 5-year period ending in 1985 from 323 consecutive patients with liver injury caused exclusively by blunt trauma treated at Maryland Institute for Emergency Medical Services Systems, Shock Trauma Center, a regional center for major trauma. It is a combined experience of an institutional staff of trauma surgeons.

Patient Profile

There were 211 males (65%) and 112 females (35%) comprising 3.48% of 9271 patients admitted during this period. The average age was 29 years. Automobile accidents accounted for 79%, motorcycles 10%, and pedestrians 8% of the injuries. The remaining 3% resulted from industrial, farm, or home accidents. Thirty per cent of these patients had abnormal elevation of their blood alcohol on admission. Except for a few patients from the immediate urban center who came by ambulance, the majority of these patients were transported directly from the scene of the accident by helicopter and

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transferred to the admitting area where immediate resuscitation, diagnostic evaluation, and management protocols were instituted by full-time traumatologists. Any patient who had injury to other systems, namely, closed head injuries, fractures of the skeleton, blunt chest injury, maxillofacial trauma, or extensive soft tissue contusion that could require a prolonged general anesthesia during their care, or who may have been unable to react reliably with normal physical signs because of inhibition by alcohol or other drugs, or were hemodynamically unstable, as well as those with clinical signs that led to the suspicion that there was organ injury within the abdomen, were subjected to diagnostic peritoneal lavage. The diagnosis of hemoperitoneum was established using diagnostic peritoneal lavage alone, except in seven instances wherein the urgency of the patient's condition precluded it and *diagnostic* celiotomy was carried out. Another four patients were transferred from other hospitals after celiotomy disclosed liver injury deemed beyond the capability of those facilities. With an occasional exception, criteria for celiotomy was 50,000 red blood cells/mL^3 in the effluence of the diagnostic lavage.

Results

Group I-S (Table 1) consisted of 120 survivors (37%) who in the opinion of the operating surgeon required no surgical intervention to the liver at the time of the celiotomy. Injuries in this group were described by the surgeons as minor capsular tears, minor lacerations, lacerations with clots in place, not bleeding, or bleeding controlled with pressure, *etc.* In analyzing these patients other distinctive features became apparent. Ninety-seven patients (81%) were hemodynamically stable at the time of admission, with systolic blood pressure greater than 90 mmHg and pulse less than 110/min. An average of 3 units (U) of blood was given during the admission and perioperative periods. The use of drains was studied as related to complications, slightly more than half (56%) had no drains. The average stay in the hospital was 15.15 days, excluding patients with prolonged stays for closed head injury or complicated orthopedic problems.

The 60 patients in group II-S (Table 2) (18.5%) were treated using simple surgical techniques such as the placement of simple or mattress sutures, topical hemostatic agents, or both. They were slightly less hemodynamically stable (75%) than those patients in group I-S and required an average of 6 U of blood during the resuscitative and perioperative periods. Two thirds were not drained, and a one day longer hospital stay was recorded for these patients.

Forty-two patients (13%) were assigned to group III-S (Table 3). Patients so designated were more severely injured and required more aggressive surgical measures. Seventy-four per cent of these patients were hemodynamically unstable at the time of admission. Three fourths had associated extra-abdominal injuries, including thoracic in 26 patients, orthopedic in 16 patients, maxillofacial in 13 patients, and neurologic in 11 patients. Associated abdominal injuries, spleen in 16 patients, pancreas in 4 patients, bowel in 3 patients, gallbladder in 3 patients, and diaphragm in 2 patients occurred in half of the patients. The clear difference from survivors in groups I-S and II-S appeared to be the amount of blood replacement. Excluding one patient who used 100 U of whole blood, an average of 22 U of PRBCs per patient was given. Fresh frozen plasma was used liberally in this group of patients to enhance blood clotting. Drains were not used in 30% of this group. The hospitalization increased to 24 days if two patients with prolonged stays are excluded. The only three survivors of hepatic artery ligation are in this group. Fifteen patients had some degree of liver resection, limited in all instances to resectional debridement of the injured fragment of the liver. Suture technique was the most often used and most effective method of gaining control of the hemorrhage. One patient was treated successfully with packing only of a major liver injury. Thirty of the 42 patients in this group recovered without complications related to the abdomen.

The 17 patients (5.26%) in group I-D (Table 4) were clinically similar to those in group III-S except that they died. Though the liver was considered to be a major factor in the death of these patients, this is primarily based on the impression that the extensive blood loss from the liver and the accompanying shock aggravated the recovery of other organ functions. Excluding two patients with 105 days and 125 days, respectively, the interval between injury and death in these patients averaged 12.5 days. Seven patients had either the right or the left hepatic artery ligated and in one patient the common hepatic artery was ligated. Death in this group of 17 patients often followed the sequence of fever, increased cardiac output, and peripheral vasodilatation characteristic of sepsis, resulting in progressive multiorgan failure and eventual death, or failure to control the liver hemorrhage in the face of refractory coagulopathy.

Group II-D (Table 5) includes 42 patients (13%) who died intraoperatively because of failure to control the bleeding from a severely injured liver. All had associated major injuries requiring operative treatment. Thirty-seven patients had 49 extra-abdominal injuries including severe crushing chest injuries (*i.e.*, lacerated lung, myocardial contusion, and ruptured diaphragms in 23

TABLE 1. *Survivors Group I-S: Patients with Minor Liver Injury, No Treatment to Liver Required (N = 120)*

	N
Sex ratio	
M:F	2.24:1
Admission vital signs	
Stable	97
Unstable	23
Units of blood given at admission and perioperatively	
Average per patient	2.98
Abdominal complications with or without drains	
No drains, no complications	66
Drained, without complications	44
Drained, with complications*	8
Not drained, with complications†	2
Average stay in hospital in days‡	15.15

* 2 wound infections, 2 wound dehiscences, 2 left subphrenic abscesses, 2 small bowel perforations.

† 1 Staphylococcus fascitis and wound dehiscence, 1 postraumatic pancreatitis.

‡ Patients with severe closed head injury and complicated orthopedic injuries are not included in the average.

TABLE 3. *Survivors Group III-S: Patients with Severe Liver Trauma Treated with Conventional Surgical Methods (N = 42)*

Sex ratio	
M:F	2:1
Admission vital signs	
Stable	11
Unstable	31
Units of blood given at admission and perioperatively (excluding 1 patient receiving 100 U)	
Average per patient	22
Dominant surgical intervention used at operation	
Suture alone	20
Resectional debridement (partial lobectomy)	15
Packing alone	1
Combination of methods above	6
Abdominal complications with or without drains	
No drains, no complications	13
Drained, without complications	17
Drained, with complications†	10
Complications without drains‡	2
Average stay in hospital in days§	24.12

* Hepatic artery ligation was employed in three patients.

† 7 subphrenic abscesses. 3 wound dehiscences.

‡ 1 wound dehiscence, 1 reoperative bleeding.

§ Two patients with closed head injury with stays of 115 and 134 days are excluded.

TABLE 5. *Deaths Group II-D: Intraoperative Deaths from Severe Liver Trauma (N = 42)*

Sex ratio	
M:F	3:1
Admission vital signs	
Stable	2
Unstable	40
Units of blood infused before death	
Average per patient	28.5
Dominant surgical attempt to salvage	
Suturing in combination with other measures	11
Packing (compression of injury site)	12
Formal hepatic lobectomy	9
Intracaval shunting	7
Resectional debridement	3
Common hepatic artery ligation	2
Right hepatic artery ligation	2
Death before effective measures were started	6

TABLE 2. *Survivors Group II-S: Patients with Moderate Liver Injury, Minimal Surgical Treatment Required (N = 60)*

Sex ratio	
M:F	2:1
Admission vital signs	
Stable	45
Unstable	15
Units of blood given at admission and perioperatively	
Average per patient	5.92
Methods of intraoperative surgical treatments used	
Suture technique*	50
Cautery alone	3
Packing (removed before closing celiotomy)	2
Hemostatic agent alone or in combination with above	10
Abdominal complications with or without drains	
No drains, no complications	37
Drained, without complications	15
Drained, with complications†	6
Complications without drains‡	2
Average stay in hospital in days§	15.88

* Usually simple or mattress interrupted chromic cat gut on a swaged on liver blunt point needle.

† 1 wound dehiscence, 2 left subphrenic abscesses; 1 reoperation bleeding, 2 wound infections.

‡ 2 wound infections.

§ Patients with severe closed head injury and complicated orthopedic injuries are not included in the average.

TABLE 4. *Deaths Group I-D: Late Deaths from Severe Liver Trauma (N = 17)*

Sex ratio	
M:F	4.25:1
Admission vital sign	
Stable	10
Unstable	7
Units of blood given at admission and perioperatively (excluding 1 patient receiving 191 U)	
Average per patient	37
Dominant surgical intervention used at operation	
Suture alone	6
Resectional debridement	5
Packs in combination with either of above	3
Hepatic artery ligation with other procedures	7
Drains*	
Drained	14
Not drained	3
Abdominal sepsis present in patients with drains	4
Abdominal sepsis present in undrained patients	3
Hospitalization interval in days before death†	12.53

* Sepsis and/or multiorgan failure was present in all patients at the time of death.

† Excluding two patients with 105 and 125 days.

TABLE 6. *Deaths Group III-D: Patients with Insignificant Liver Trauma Dying As a Result of Associated Trauma (N = 42)*

Sex ratio	
M:F	0.75:1
Admission vital signs	
Stable	15
Unstable	27
Ultimate cause of death	
Closed head injury	33
Severe cardiac contusion	3
Pulmonary contusion	2
Cardiac arrest, cause unexplained	2
Massive exsanguination from pelvic fracture	1
Thoracic aortic rupture	1
Average hospital interval before death in days	6.8

patients). In 13 patients closed head injury may have been as grave as the liver injury, but it was deemed the liver injury alone would likely have been fatal. Concurrent abdominal injuries were present in 17 patients including spleen in 12 patients, bowel in 5, and kidney, bladder, and gallbladder in 1 patient each. Only two of these patients were hemodynamically stable on arrival in the admitting area. Twelve patients (29%) arrived in the admitting area with no obtainable blood pressure, and 11 had systolic blood pressures < 70 mmHg. In those 27 patients in whom prothrombin time studies were available at the time of admission, there was a marked prolongation (greater than 3 seconds over control) in 21 (75%). These injuries were described as deep stellate lacerations or transections, 34 (81%) primarily involving the right hepatic lobe. In 16 patients (38%) the injury involved the major hepatic veins or retrohepatic vena cava. Intracaval shunting of the inferior vena cava was unsuccessfully attempted seven times. The common hepatic artery was ligated twice and the right hepatic artery twice. On seven occasions formal anatomic resections of the right lobe were initiated. Twelve patients expired while attempts were made to compress the liver in order to achieve hemodynamic stability, and six patients expired before any attempt at control could be made.

Group III-D (Table 6) contains deaths primarily associated with injuries to other organ systems. It is noteworthy that 24 of these patients were female, a sex ratio of 0.75:1 (M:F). From the data available for this study, there is no clear reason for this skewed statistic. The position of the victim in the vehicle was studied with no significant finding between driver and passenger. These 42 patients (13%) are predominantly patients with closed head injury and an incidental liver injury, which was insignificant. Fatal head injury occurred in 33 of these patients and was a major contributing factor in an additional nine patients. Severe chest injury was also prominent. Eighteen of these patients (43%) died in the operating room or on the day of admission, and 76% died within the first week.

Two hundred forty patients were studied regarding the use of intra-abdominal drainage; the 42 patients who died on the operating table and 42 who died from injury unrelated to the abdomen were excluded. Intra-abdominal drainage was established in 116 (48%), and no drainage was used in 124 (52%) (Table 7). These usually consisted of either penrose or sump drains, or a combination of both, brought out through separate wounds. The infection rate in the 116 patients who were drained was 22% *versus* a 4% rate in 124 patients not drained (p < 0.00002, Fisher's exact test, two-tailed). The instinct because of traditional training of most surgeons has been to use drains in the more severely injured patients, which is also reflected in this study. Of the 17 patients who died late, (group I-D) all but three were drained. There was infection in four of the 14 patients drained and in one of the three not drained (NS). Of the 43 patients with severe liver injury that survived (group III-S), 29 were drained and eight had complications likely associated with prolonged drainage. The 14 patients not drained had no complications (p < 0.04). In the 180 patients with minor liver injury (groups I-S and II-S), 14 patients had infections attributable to drains *versus* four infections in the undrained patients (p < 0.02). The theoretical occurrence of bile peritonitis or collections of intra-abdominal bile did not occur and T tube drainage of the common bile duct was not used.

TABLE 7. *Relationship Between Drainage and Incidence of Abdominal Complications*

Group	Drained (%)	Infections (%)	Not Drained (%)	Infections (%)
I-S	52/120 (43)	8/52 (15)*	68/120 (57)	2/68 (3)
II-S	21/60 (35)	6/21 (29)†	39/60 (65)	2/39 (5)
III-S	27/42 (64)	10/27 (37)‡	15/42 (36)	2/15 (13)
I-D	14/17 (82)	4/14 (29)§	3/17 (18)	3/3 (100)
Total	114/239 (48)	28/114 (26)‖	125/239 (52)	9/125 (4)

* p < 0.02.
† p < 0.02.
‡ p < 0.04.
§ NS.
‖p < 0.00002, Fisher's exact test, two-tailed.

In this study of 323 patients with injury to the liver that varied from incidental and insignificant to severe and fatal, 101 died, a 31.12% mortality rate. A more accurate perspective of the magnitude of the problem of management of severe blunt liver trauma can be appreciated if the 180 patients without significant liver injury (groups I-S and II-S) are excluded from the study, and the 42 patients with minor liver injury that died from the associated injury are not included (group III-D) in the total of 222 patients. Among the 101 remaining patients with severe liver injury there were 42 survivors (group III-S). There were 17 late deaths (group I-D) and 42 patients (group II-D) who died during the operation because of failure to control the hemorrhage from liver injury. These 101 patients were the patients with liver injury that were theoretically salvageable at the time of admission. Thus, the mortality rate for the liver severely injured by blunt trauma in this study is 58.4%. However, the 17 late deaths (group I-D) of those with severe injury from blunt trauma represent a mortality rate of 5.26% of the total 323. Many of the 42 intraoperative deaths and the 42 deaths from associated injury (groups II-D and

III-D) realistically and probably had little chance for survival at the time they were admitted. It is the operative management of the bleeding liver in these patients that is the real challenge to those treating severe blunt liver trauma and provides the focus of this study.

Discussion

Myriads of measures to deal with serious liver injury have been proposed, used, studied, and reported by respected investigators from outstanding institutions worldwide. No one surgical technique has emerged that is clearly superior and applicable to every patient. Each has proponents, and when expertly applied in the correct situations will have rewarding results.

Suturing

Suturing the liver has been condemned by Lim et al.,[2] and according to Mays[3] is based on tradition only. Trunkey, et al.[4] reporting on 811 patients, noted that 20.4% of their patients with extensive laceration of the liver were treated using 0 to number 1 catgut interlocking horizontal mattress sutures. During the latter part of their study bleeding points were managed by direct suture ligation. It was thought that this reduced the chance of necrosis and hemobilia. Only 21.3% of the 811 patients they reported were victims of blunt trauma.

In this study suturing the liver as described above, with variations according to the operator's perference, was the technique most often used. All of the 60 patients in group II-S and 26 of the 42 in group III-S were treated using various suturing methods. In blunt trauma, where two fragments of liver gape apart and where point ligation of the bleeding vessels would require manipulative intervention, often difficult because of poor exposure and the technical maneuvering that adds to the trauma already present, this simple, quick, traditional method was effective in limiting blood loss. We experienced none of the complications often alluded to (*i.e.*, hemobilia or liver necrosis in the survival group) when sutures were used. Lucas and Ledgerwood[5] noted that "contrary to theoretical objections that liver sutures will cause hepatic ischemia . . . no patient died following liver suture for control of bleeding," only 9% of the patients in that study were victims of blunt injury.

Liver Resection

Successful liver resection in 15 surviving patients in group III-S was limited to removal of the injured fragments peripheral to the fracture line of the liver. *Resectional debridement, completion resection,* and *segmentectomy* were terms used to describe these procedures. Two patients required reoperation for bleeding and were treated with additional ligations of the right hepatic arteries. Both patients developed abscesses, presumably related to the relative ischemia of the liver. Major liver resection along anatomic planes advocated by many[6-11] was attempted nine times and was never successfully accomplished with a survivor (group II-D). Each of these nine patients was stable prior to the commencement of the attempted formal resection, and as the procedure progressed the bleeding became uncontrollable. Mays[3] in his monograph on hepatic trauma, referring to the use of anatomic lobectomy in acute liver injury states "the mortality rate forbids it." Pachter and Spencer[12] noted a mortality above 50% and observed "though the techniques of hepatic resection have been well defined there is declining frequency in its use." The present experience here with blunt trauma substantiates these warnings.

Intracaval Shunting

Schrock et al.[13] described the use of an intracaval shunt of the inferior vena cava in a victim of a fall with avulsion of the hepatic veins and a lacerated retrohepatic inferior vena cava. Since that report Doty and Berman[14] and Brajendranath et al.[15] among others have added technical refinements in search of the best approach to achieving vascular control when injury to the liver extends into the retrohepatic vena cava or the hepatic veins. Some authors oppose intracaval shunting. Yellin et al.[16] advocate venous isolation with occlusion of the inflow to the liver. Balasegaram[17] had eight survivors in 12 patients with *juxtahepatic venous* injury using venous isolation and contends that sternotomy to gain exposure takes too much time in these desperate circumstances. Regardless, if access to the suprahepatic vena cava is necessary, sternotomy easily allows the quickest exposure with the least postoperative morbidity rate.

Intracaval shunting was used in seven patients (group II-D) without a survivor. All three approaches usually described for the insertion of the shunt were utilized. Patients with these injuries generally do not do well in spite of isolated reports of successful use of either of these methods.[18]

Ligation of Arterial Inflow

In 1933 Graham and Cannell[19] postulated that operative interruption of the hepatic artery could be successfully done without interfering with liver viability. Hepatic artery ligation was briefly in vogue as a treatment for cirrhosis after being introduced by Rienhoff[20] in 1951. Madding[21] in 1954 suggested that hepatic artery ligation be "used in some cases of liver injury." Mays[22,23] has recently promulgated *dearterialization* of the liver in severe injury with certain limits in selected patients. Others[24–26] also saw a place for its use. Still others, Pachter and Spencer,[27] see it as an unnecessary hazard for the patient and it is without clear rationale.

In this review, two patients with right hepatic artery ligation and one patient with ligation of the proper hepatic artery survived (group III-S). There were also four patients with hepatic artery ligation among those that died intraoperatively (group II-D). Of the 17 late deaths from liver injury (group I-D), seven had hepatic artery ligation. Both surviving patients with right hepatic artery ligation required reoperation for continued bleeding. The third survivor with ligation of the proper hepatic artery had an uncomplicated recovery and was discharged in 21 days. The records here show one unqualified success in 14 patients with hepatic artery ligation.

Omental Packing

Stone and Lamb[28] described the use of an isolated omental pedicle placed into the fracture defect and held in place by sutures. An updated report by Fabian and Stone[29] described their experience with 115 patients in which this method of packing to obtain hemostatic control was successful 90% of the time. The experience in this study with omental packing is limited to one patient (group III-S) where it was successful.

Packing with Gauze

A last desperate measure to control bleeding from the liver, packing with gauze, has recently under certain conditions been proposed as a deliberately planned first approach.[30,31] Packing with radiopaque laparotomy pads was used on six occasions, three times in the survivors' group without complications, and three times in the late death group. Two of the late death group developed infection and sepsis before they died.

Drains and Complications

The association between the use of intra-abdominal drainage and infection was analyzed (Table 7). While the traditional teaching of most surgeons is that drainage of hepatic injuries is necessary in order to avoid bile peritonitis and abscess formation, these data do not bear this out. The incidence of intra-abdominal infectious complications was significantly greater in those patients who were drained compared to those who were not ($p < 0.00002$). This may be related to the fact that the mechanism of injury in this series was blunt trauma rather than penetrating trauma, and, therefore, the operative field was less likely to be contaminated. While there are situations encountered in these kinds of patients that may dictate the use of drainage, from this study the evidence against routine use of drains in blunt liver trauma would support those who believe it is not necessary, especially in situations of insignificant liver injury.[32,33]

Conclusions

Though the data presented in this study has been subjected to retrospective analysis, it was accumulated in a prospective fashion. Specific management trials were to be scrutinized and documented. Was hepatic artery ligation helpful? Was major hepatic resection useful? Could intracaval shunting be successfully used? What about drains? Does packing have a place? When does coagulopathy and/or hemodilution become irreversible? These among other questions formed the basis to begin this study; as the data were collected and analyzed on a yearly basis other problems in the care of the liver injured by blunt trauma became apparent.

Before the study began it was clear that serious injury to the liver was a difficult condition, and both the surgical team and the patient had usually encountered a desperate situation. There was no concensus among the staff as to the best approach to these problems. As the foregoing material indicates, the entire spectrum of known technical approaches have been utilized with varying degrees of success and without decisive results favoring any one approach. As each success or failure was encountered and documented, there was a gradual realization among the staff that the more aggressive approaches were most often futile, and there was a trend toward less bold surgical measures. The attending surgeons became less inclined to attempt formal anatomic resections. Hepatic artery ligation, at times a technical challenge itself, did not always stop the bleeding and there were no instances where intracaval shunting was successful. Though these heroic measures have had persuasive advocates, the impression in the literature that these are simple procedures that can simply be accomplished in instances of severe liver trauma is misleading and has at times contributed to a novice, machismo approach to major liver trauma.

The liver injured by blunt trauma and the associated injury, both extra-abdominal and abdominal, when it occurs creates a clinical entity requiring special considerations and the best in clinical judgment and surgical management. Severe blunt trauma must be considered a specific disease. There are few conditions that acutely alter the entire physiology as does blunt trauma in its most serious forms. The mortality rate from liver trauma bears a linear relationship to the severity of the injury and an inverse relationship to the experience, judgment, and skill of the team caring for the patient. These disasters seem to occur at night and on weekends. Since the best results reported come from institutions where one doctor concentrates on the liver only, or a liver team is organized, it may occasionally be well to stay the definitive execution of care (or pack the injury) until such a team can be assembled.[34]

On admission most of these patients with severe liver injury will have gross blood return on diagnostic peritoneal lavage. They will usually be hemodynamically unstable as was seen in this study. Before attempts to treat specific organ injury are begun, effective restitution of cellular oxygenation must be accomplished through respiratory and cardiac support by whatever means are required. In most instances severe liver injury will become the priority consideration in the management of the severely injured trauma victim.

At operation, minor injuries need little or no treatment. The more severe injuries graded toward those with retrohepatic vena caval injury or hepatic vein involvement require only those measures needed to control bleeding. From these data the great majority can be controlled with simple sutures placed 2 to 3 cm from the edge of the fracture with an absorbable suture using a blunt point needle with a large arc placed in whatever fashion the operator is comfortable with. The anxiety about intrahepatic hematoma, hemobilia, necrosis along the suture line, bile collection, and biliary fistulae appear to be unwarranted; they did not occur in this series. The more peripheral these injuries are, the better. These simple methods work, and if done with a minimum of meddling, will save blood and time. Drainage of the abdomen in these relatively minor injuries does not appear warranted in lieu of the increased incidence of infectious complications.

In the surgical management of fragmentation fractures where the viability of distal segment of the liver is questionable, resectional debridement is all that is necessary or should be attempted. Formal or anatomic lobectomy should not be attempted, and hepatic artery ligation is rarely helpful. Bleeding points should be individually controlled by suture ligatures in preference to hemoclips or cautery since repeated *mopping* with gauze tends to pull off the clips and abrade the eschars of the cautery. These procedures can be tedious and time-consuming. Impatience and continuing to operate in the face of persistent bleeding is not often rewarded by a successful outcome. The patients must be hemodynamically stable, if possible, before any attempts at technical maneuvering are accomplished. For deeper, more central injuries, if bleeding is arterial or is too great to ignore, control at the porta hepatis using Pringle's maneuver and widening the *hepatotomy* to control the bleeding vessels with point ligations may be necessary. In addition, compression of the liver injury to control the bleeding while waiting for the replacement of blood and clotting factors seems an easy thing to do but is often ignored. When there is a blood clot in the fracture fissure, it is a good idea to *dry up* the area and ascertain the degree of bleeding and if possible, in good judgment, to leave it alone before the curiosity to probe the depth of the wound becomes a hazard. In these kinds of lesions packing with laparotomy pads carefully placed between the liver and the diaphragm and then stabilized with several packs in the subhepatic space will often be sufficient treatment. No drains are used, and after several days when the patient has been stabilized, the packs, residual blood, and debris are removed at reoperation. Though the experience in this study with omental packing is nil, there are some sound theoretical considerations for its use.[28,29] Again, even in these large injuries (groups III-S and III-D), bile-related complications did not occur and the incidence of infectious complications associated with the use of drains was significantly increased ($p < 0.01$).

Data accumulated on blood coagulation in this study indicate that coagulation factors were depressed in the majority of the severely injured patients. After patients with suspected severe liver injury are admitted, and as soon as possible during the resuscitative process, fresh frozen plasma should be given. There comes a critical point in the bleeding when the clotting factors become depleted and whatever name is applied to the syndrome, at that moment, the patient's clotting time is extended to infinity. Though this could not always be clearly documented, this point usually comes after six to eight transfusions of red blood cells, whether stored blood or autotransfusion is used. When this point is recognized, the better alternative to further frustration may well be to pack the site and resort to replacement of red blood cells and clotting factors in a carefully monitored intensive care environment. Presently in this country the use of component blood products is becoming standard practice, and the luxury of fresh whole blood is becoming a thing of the past. Fresh frozen plasma, cryoprecipitate, and platelets, as indicated, should be used early in the care of these patients, and continued through the postoperative period. The liver is the site of production of these factors, and presumably has been functionally impaired by the injury. This coagulopathy is amplified by hypothermia, which occurs commonly after massive transfusion of cold blood and blood products. Maintenance of normothermia is essential in these patients, and the use of efficient, high performance, simple blood warmers is sorely needed. Such a device has recently been described[35]; however, its clinical efficacy remains unproven.

Our experience with injuries involving the retrohepatic vena cava previously described is similar to that of Walt.[18] Only when these injuries can be anticipated and suspected, and the patients' clinical condition allows time for deliberate planning, do the shunting and inflow bypass procedures stand a real chance of being successful. At present, the best approach to juxtahepatic vascular injuries appears to be that of Pachter et al.,[36] who advocate external cooling of the liver, use of large doses of steroids, occlusion of hepatic inflow, and a direct approach to the injury through the liver, if necessary, using the *finger fracture* technique and point ligation of bleeding vessels. Until better preoperative recognition is achieved, such as through the efforts of Federle et al.[37] using computed tomography, immediately available in the resuscitation area, or until technical advances in surgery occur making it possible to isolate the liver easily from its vasculature so that necessary repairs can be made in a dry operating field, mortality rates with these injuries will continue to be high.

There have been impressive advances in the care of these critically injured patients especially in the area of intensive management, in control of sepsis, pulmonary care, nutrition, anesthesia, and technical instrumentation in monitoring. In trauma centers that care for civil trauma, the concept of a dedicated liver team alluded to by Spencer[38] should be seriously considered. Other considerations might be the use of external pump bypass set up in advance for suspected severe liver injury or the routine insertion of an intracaval shunt easily placed through a groin vein before the abdomen is opened.[39] Advances must continue to be made in safety standards for the roads and highways. There must be insistence by traumatologists that our government pass legislation to require air bags or equivalent restraints. The people who should be wearing seat belts just do not wear them!

Summary

This is a study of 323 patients from a major trauma center of liver injury caused exclusively by blunt trauma. The entire spectrum of known technical interventions to control liver hemorrhage were utilized by the full-time staff of traumatologists. A mortality rate of 58.4% on 101 patients with marked hemorrhage from the severely injured liver is noted. This is in the range noted in other studies.[13] Overall, the mortality rate for the 323 patients was 31% and for those who died from liver injury if they survived the celiotomy (17 patients) the mortality rate was 5.26%. Conservatism in the management of the more seriously injured patients is supported by the statistics collected during the study. Liberal replacement of blood clotting factors is advocated. Earlier consideration of packing to the liver might reduce the formidable mortality rates in those patients with serious injury. Dedicated liver trauma teams in institutions, where feasible, is encouraged.

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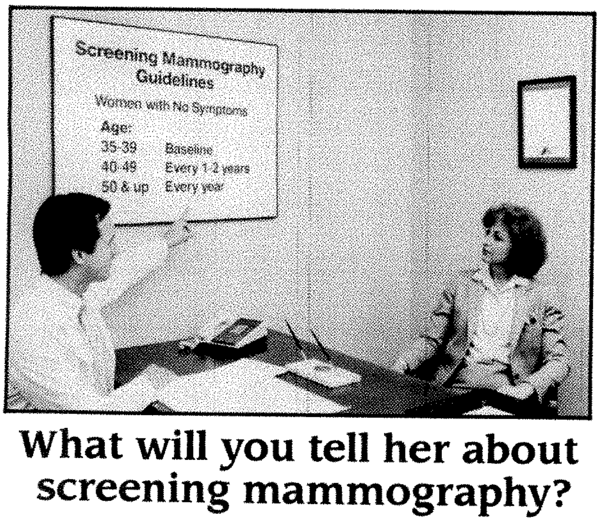

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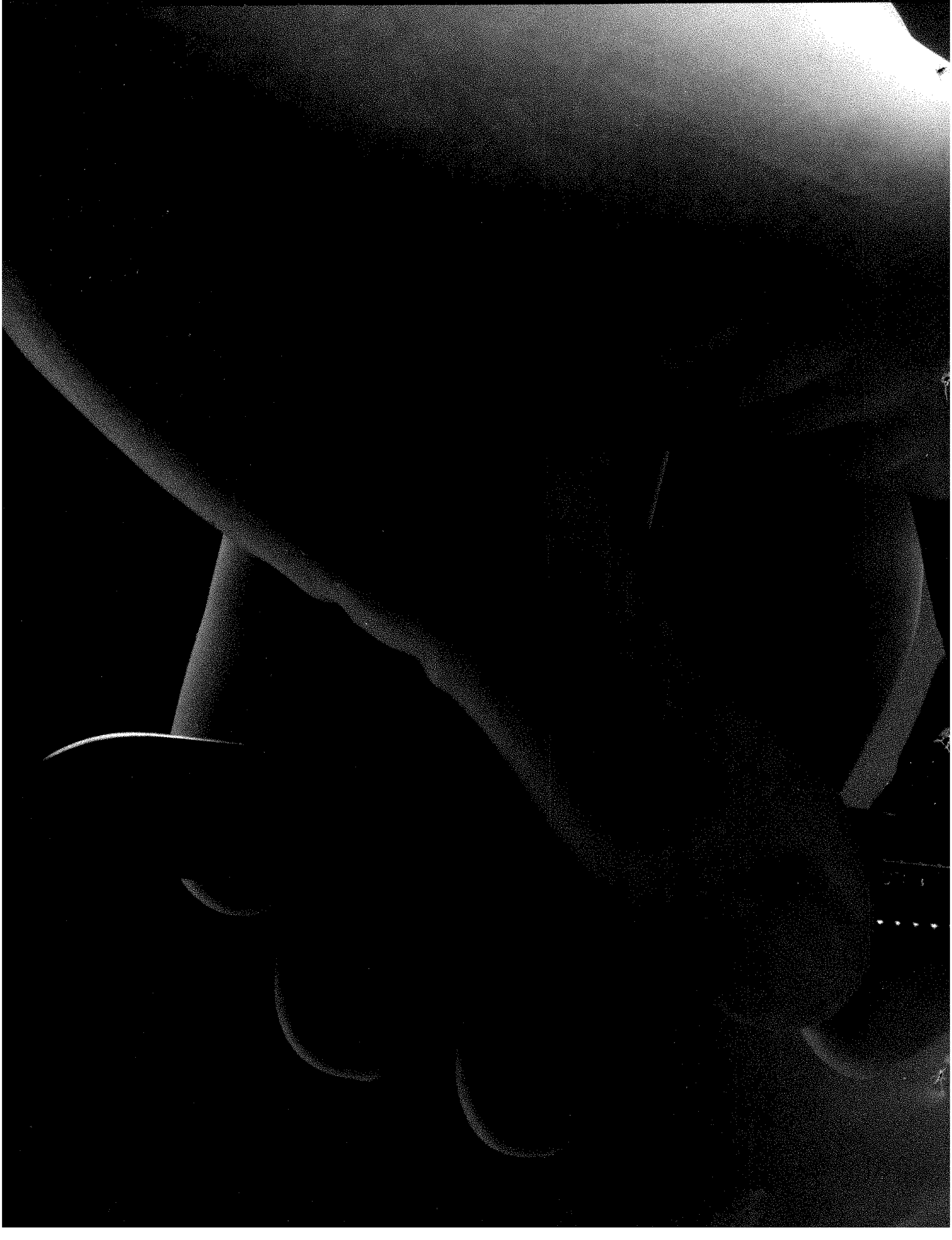

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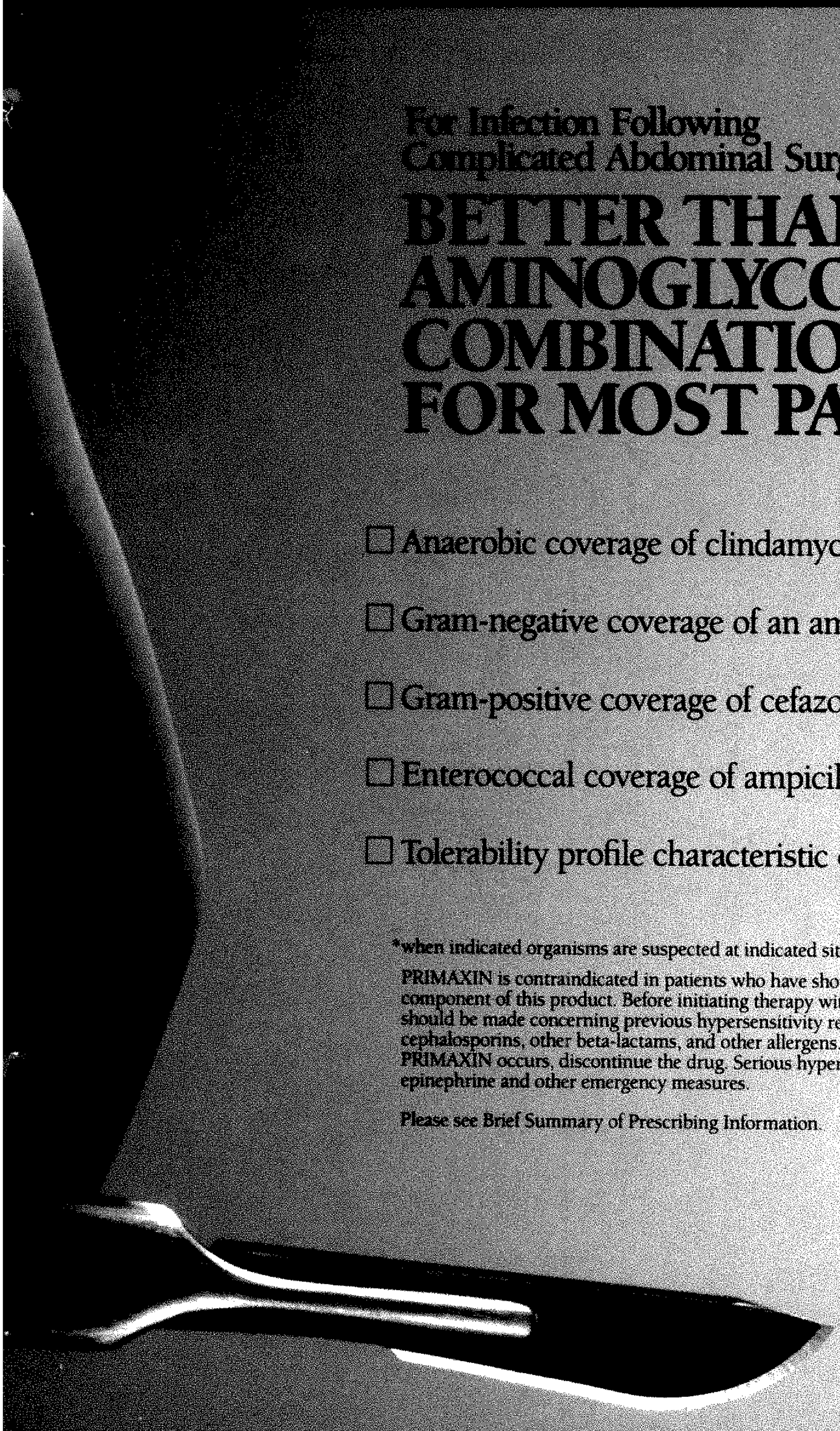

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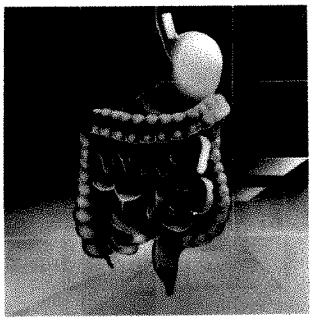

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Warnings: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH BETA LACTAMS. THESE REACTIONS ARE MORE APT TO OCCUR IN PERSONS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER BETA LACTAM. BEFORE INITIATING THERAPY WITH 'PRIMAXIN,' CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA LACTAMS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION TO 'PRIMAXIN' OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with virtually all antibiotics, including PRIMAXIN; therefore it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. This colitis may range in severity from mild to life threatening.

Mild cases of pseudomembranous colitis may respond to drug discontinuance alone. In more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte, and protein supplementation, and the use of a drug such as oral vancomycin, as indicated. Isolation of the patient may be advisable. Other causes of colitis should also be considered.

Precautions: *General*—CNS adverse experiences such as confusional states, myoclonic activity, and seizures have been reported during treatment with PRIMAXIN, especially when recommended dosages were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. However, there have been reports of CNS adverse experiences in patients who had no recognized or documented underlying CNS disorder or compromised renal function.

Patients with severe or marked impairment of renal function, whether or not undergoing hemodialysis, had a higher risk of seizure activity when receiving maximum recommended doses than those with no impairment of renal function; therefore, maximum recommended doses should be used only where clearly indicated (see DOSAGE AND ADMINISTRATION).

Patients with creatinine clearances of ≤ 5 mL/min/1.73 m^2 should not receive PRIMAXIN unless hemodialysis is instituted within 48 hours.

For patients on hemodialysis, PRIMAXIN is recommended only when the benefit outweighs the potential risk of seizures.

Close adherence to the recommended dosage and dosage schedules is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of PRIMAXIN re-examined to determine whether it should be decreased or the antibiotic discontinued.

As with other antibiotics, prolonged use of PRIMAXIN may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken. While PRIMAXIN possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system function during prolonged therapy is advisable.

Drug Interactions—Since concomitant administration of PRIMAXIN and probenecid results in only minimal increases in plasma levels of imipenem and plasma half-life, it is not recommended that probenecid be given with PRIMAXIN.

PRIMAXIN should not be mixed with or physically added to other antibiotics. However, PRIMAXIN may be administered concomitantly with other antibiotics, such as aminoglycosides.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Gene toxicity studies were performed in a variety of bacterial and mammalian tests *in vivo* and *in vitro*. The tests were: V79 mammalian cell mutation assay (PRIMAXIN alone and imipenem alone), Ames test (cilastatin sodium alone), unscheduled DNA synthesis assay (PRIMAXIN), and *in vivo* mouse cytogenicity test (PRIMAXIN). None of these tests showed any evidence of genetic damage.

Reproduction tests in male and female rats were performed with PRIMAXIN at dosage levels up to 8 times the usual human dose. Slight decreases in live fetal body weight were restricted to the highest dosage level. No other adverse effects were observed on fertility, reproductive performance, fetal viability, growth, or postnatal development of pups. Similarly, no adverse effects on the fetus or on lactation were observed when PRIMAXIN was administered to rats late in gestation.

Pregnancy—Pregnancy Category C: Teratogenicity studies with cilastatin sodium in rabbits and rats at 10 and 33 times the usual human dose, respectively, showed no evidence of adverse effect on the fetus. No evidence of teratogenicity or adverse effect on postnatal growth or behavior was observed in rats given imipenem at dosage levels up to 30 times the usual human dose. Similarly, no evidence of adverse effect on the fetus was observed in teratology studies in rabbits with imipenem at dosage levels at the usual human dose.

Teratology studies with PRIMAXIN at doses up to 11 times the usual human dose in pregnant mice and rats during the period of major organogenesis revealed no evidence of teratogenicity.

Data from preliminary studies suggest an apparent intolerance to PRIMAXIN (including emesis, inappetence, body weight loss, diarrhea, and death) at doses equivalent to the average human dose in pregnant rabbits and cynomolgus monkeys that is not seen in non-pregnant animals in these or other species. In other studies, PRIMAXIN was well tolerated in equivalent or higher doses (up to 11 times the average human dose) in pregnant rats and mice. Further studies are under way to evaluate these findings.

There are, however, no adequate and well-controlled studies in pregnant women. PRIMAXIN should be used only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRIMAXIN is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in infants and children below 12 years of age have not yet been established.

Adverse Reactions: PRIMAXIN is generally well tolerated. Many of the 1,723 patients treated in clinical trials were severely ill and had multiple background diseases and physiological impairments, making it difficult to determine causal relationship of adverse experiences to therapy with PRIMAXIN.

Local Adverse Reactions—Local adverse clinical reactions that were reported as possibly, probably, or definitely related to therapy with PRIMAXIN were: phlebitis/thrombophlebitis (3.1%), pain at the injection site (0.7%), erythema at the injection site (0.4%), vein induration (0.2%), infused vein infection (0.1%).

Systemic Adverse Reactions—The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to PRIMAXIN were: nausea (2.0%), diarrhea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%) (see PRECAUTIONS), dizziness (0.3%), pruritus (0.3%), urticaria (0.2%), somnolence (0.2%).

Additional adverse systemic clinical reactions reported as possibly, probably, or definitely drug related occurring in less than 0.2% of the patients or reported since the drug was marketed are listed within each body system in order of decreasing severity: *Gastrointestinal*—pseudomembranous colitis (see WARNINGS), hemorrhagic colitis, gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, heartburn, pharyngeal pain, increased salivation; *CNS*—encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, psychic disturbances; *Special Senses*—transient hearing loss in patients with impaired hearing, tinnitus; *Respiratory*—chest discomfort, dyspnea, hyperventilation, thoracic spine pain; *Cardiovascular*—palpitations, tachycardia; *Renal*—oliguria/anuria, polyuria; *Skin*—erythema multiforme, facial edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae; *Body as a Whole*—polyarthralgia, asthenia/weakness.

Adverse Laboratory Changes—Adverse laboratory changes without regard to drug relationship that were reported during clinical trials or reported since the drug was marketed were: *Hepatic*—increased SGPT, SGOT, alkaline phosphatase, bilirubin, and LDH; *Hemic*—increased eosinophils, positive Coombs test, decreased WBC and neutrophils, including agranulocytosis, increased WBC, increased platelets, decreased platelets, decreased hemoglobin and hematocrit, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils; *Electrolytes*—decreased serum sodium, increased potassium, increased chloride; *Renal*—increased BUN, creatinine; *Urinalysis*—presence of urine protein, urine red blood cells, urine white blood cells, urine casts, urine bilirubin, and urine urobilinogen.

NOTE: Due to the high antimicrobial activity of PRIMAXIN, it is recommended that the maximum total daily dosage not exceed 50 mg/kg/day or 4.0 g/day, whichever is lower.

How Supplied: PRIMAXIN is supplied as a sterile powder mixture in vials, infusion bottles, and single-dose ADD-Vantage®† vials containing imipenem anhydrous and cilastatin sodium as follows: 250 mg imipenem equivalent and 250 mg cilastatin equivalent; 500 mg imipenem equivalent and 500 mg cilastatin equivalent.

Caution: The suspension from vials is not for direct infusion.

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Surgical *Versus* Endoscopic Management of Common Bile Duct Stones

B. M. MILLER, M.D., R. A. KOZAREK, M.D., J. A. RYAN, JR., M.D., T. J. BALL, M.D., and L. WILLIAM TRAVERSO, M.D.

From the Departments of Surgery and Gastroenterology, Virginia Mason Medical Center, Seattle, Washington

The charts of all patients with common bile duct (CBD) stones admitted to Virginia Mason Medical Center between January 1, 1981 and July 31, 1986 were reviewed to define current methods of management and results of operative *versus* endoscopic therapy. Two hundred thirty-seven patients with CBD stones were treated. One hundred thirty patients had intact gallbladders. Of these patients, 76 (59%) underwent cholecystectomy and common bile duct exploration (CBDE) while 54 (41%) underwent endoscopic papillotomy (EP) only. Of the 107 patients admitted with recurrent stones after cholecystectomy, all but five were treated with EP. The overall mortality rate was 3.0%. Complications, success, and death rates were all similar for CBDE and EP, but the complications of EP were often serious and directly related to the procedure (GI hemorrhage, 6; duodenal perforation, 5; biliary sepsis, 4; pancreatitis, 1). Patients undergoing EP required significantly shorter hospitalization than those undergoing CBDE. Multivariate analysis showed that age greater than 70 years, technical failure, and complications increased the risk of death, regardless of procedure performed. Twenty-one per cent of those undergoing EP with gallbladders intact eventually required cholecystectomy. The conclusion is that the results of EP and CBDE are similar, and the use of EP has not reduced the mortality rates of this disease.

CARL LANGENBUCH performed the first cholecystectomy in 1882,[1] and for the first 90 years thereafter, operation formed the mainstay of therapy for benign biliary tract disease. In the early 1970s, however, techniques were developed in the fields of radiology and gastroenterology that would provide alternative therapeutic options and radically change management of biliary lithiasis. For example, in 1973 Burhenne reported fluoroscopically guided basket retrieval of common bile duct (CBD) stones via the T tube tract.[2] In 1974 Claasen and Demling from Germany[3] and Kawai from Japan[4] independently described endoscopic papillotomy (EP).

EP is performed using a lateral viewing duodenoscope. Vater's papilla is cannulated first with a diagnostic catheter, and a cholangiogram confirms the presence of stones and defines their size and location. The diagnostic catheter is then replaced with a papillotome, a diathermy wire attached to a teflon catheter. The papilla is cannulated to a variable depth, and the diathermy wire is oriented away from the pancreatic sphincter. An electrical current is passed down the wire, creating a 1- to 1½-cm incision, depending on the length of the sphincter and the size of the stones. The stones may be immediately retrieved with a Dormia basket or they may be allowed to pass spontaneously. A nasobiliary drainage catheter may be placed to prevent cholangitis if complete stone evacuation has not been accomplished.[5,6]

Initially, EP was reserved for frail patients at high risk for operation with retained or recurrent CBD stones. Early reports documented mortality rates of 1–2%[4] and major morbidity rates (pancreatitis, bleeding, and duodenal perforation) of 7–10%.[7-9] These figures compared favorably with historical surgical controls from the 1950s and 1960s when the mortality rate after operative common bile duct exploration (CBDE) was at least 5%.[10,11] Considering this comparison and the greater patient satisfaction, EP rapidly gained wide acceptance and its applications broadened. In centers where skilled endoscopists practice, EP has become the procedure of choice for recurrent stones after cholecystectomy.[12,13] In addition, it is being used with increasing frequency in

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Reprint requests and correspondence: Bonnie M. Miller, M.D., 2201 Murphy Avenue, Suite 410, Nashville, TN 37203.

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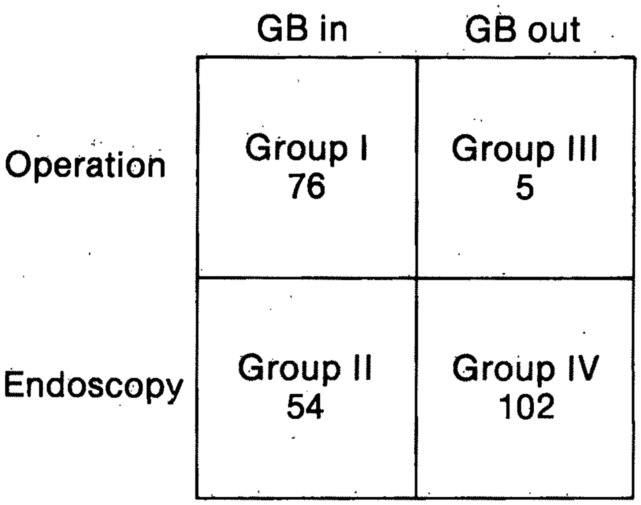

FIG. 1. Division of patients into four groups based on the presence of a gallbladder at the time of admission and initial procedure performed. Number of patients in each group is given in parentheses.

patients with intact gallbladders and common duct stones.[14]

The following report was undertaken to define the impact of EP on management of choledocholithiasis at a multispecialty referral center. Specifically, we wished to analyze how patients are initially treated, what the current results of EP and CBDE are, and whether EP has reduced the overall mortality rate of patients with CBD stones.

Patients and Methods

The Virginia Mason Medical Center (VMMC) is a multispecialty clinic located in Seattle, WA, which draws referrals from the Pacific Northwest and Alaska.

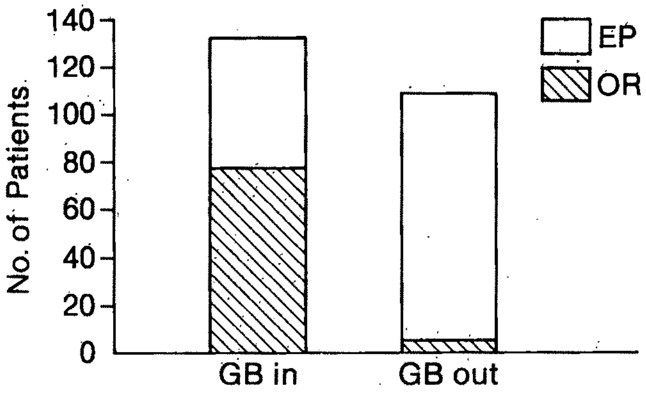

FIG. 2. Type of procedure initially performed in patients with and without gallbladders.

A computer list was generated of all patients admitted between January 1, 1981 and July 31, 1986 with the diagnosis of choledocholithiasis. The charts of these patients were screened, and only those with CBD stones documented unequivocally by retrieval or cholangiogram were included in this analysis. Two hundred thirty seven patients had common bile duct stones during this study period.

The charts of these patients were reviewed for the following data: previous cholecystectomy, procedures performed, age, year of admission, comorbid illness, acute presentation, complications, death, and technical success of procedure. In addition, patients who underwent EP without prior cholecystectomy were interviewed by telephone regarding recurrence of stones and need for subsequent procedures.

The entire population (N = 237) was divided into four groups based on two factors: the presence of a gallbladder at the time of admission and the initial procedure attempted at VMMC (Fig. 1). Patients in group I (N = 76) had intact gallbladders and underwent cholecystectomy and CBDE with or without a biliary enteric drainage procedure. Group II patients (N = 54) also had intact gallbladders, but underwent EP only as the initial procedure. Group III patients (N = 5) had undergone prior cholecystectomy and were treated with CBDE, while those in group IV (N = 102) with prior cholecystectomy underwent EP.

Statistical Analysis

The BMDP statistical package program was used for statistical analyses.[15]

Continuous variables were analyzed by analysis of variance (ANOVA).[16] A one-way ANOVA was performed to test the equality of means between two groups. This program also tests the equality of variances between the two groups (Levene's test for equal variances, a robust test computed on the absolute values of the deviations from the means).[17] Two additional one-way ANOVA statistics are also computed. Neither of these assumes the equality of variances in each group, which are: (1) the Welch statistic and (2) the Brown-Forsythe statistic.[18] These tests were used when the variances were found to be unequal between the two groups.

For multivariate analysis, Cox's logistic regression method was employed. In this model:

$$[V = \log P/1 - P = A + B_1X_1 + B_2X_2 + B_3X_3 \cdots]$$

where A represents the log odds of disease risk for a person with a standard (X = 0) set of regression vari-

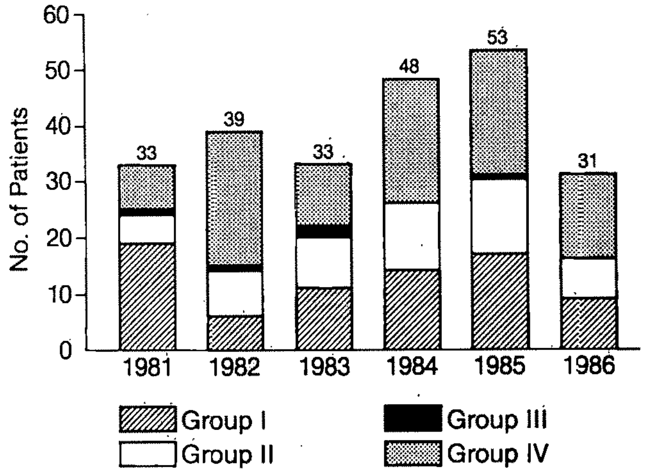

FIG. 3. Total number of patients admitted each year with CBD stones, and their distribution into the four treatment groups.

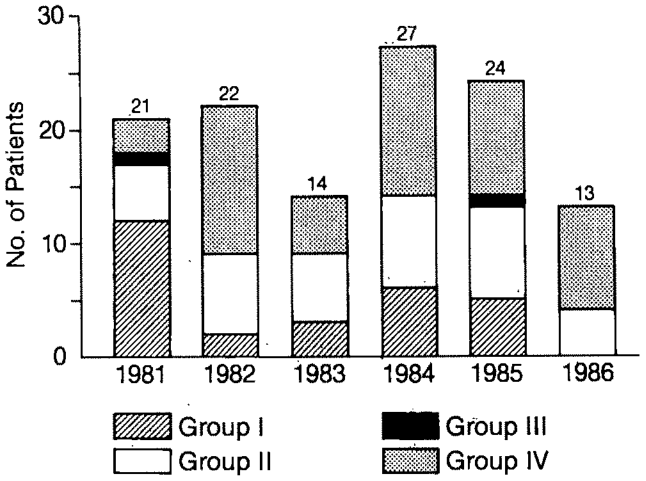

FIG. 4. The total number of patients over 70 years admitted each year with CBD stones is depicted. The patients are divided into treatment groups.

ables, while exp (B_k) is the fraction by which this risk is increased (or decreased) for every unit change in X_k.[19]

Results

Of the 237 patients, 130 had intact gallbladders (groups I and II) and 107 had retained or recurrent stones after cholecystectomy (groups III and IV). Of those with intact gallbladders, 76 underwent cholecystectomy and CBDE (59%) while 54 underwent EP (41%). Of the 107 patients who had previously undergone cholecystectomy, all but five had EP attempted as the initial procedure (Fig. 2). The number of patients with CBD stones increased during the last 3 years of the study (Fig. 3). The number of patients undergoing EP with gallbladders intact also rose during each successive year of the study, but this was in proportion to the overall increase in patients with CBD stones. The only year in which the majority of patients underwent operation was 1981 (20 out of 33). Each year thereafter, the large majority of patients underwent papillotomy.

The transition from CBDE to EP became even more apparent when examining only those patients over 70 years of age. Although the number of patients admitted per year remained stable in this age group, the number admitted for CBDE dropped sharply after 1981 (Fig. 4). For example, 12 of the 28 patients in group I who were over 70 years of age underwent operation in 1981; the remaining 16 operations were distributed fairly evenly over the next four years. The number of patients in group II over 70 years of age increased slightly over the study period, so that during the 5½ years of this review, the majority of patients over 70 with intact gallbladders underwent EP as opposed to CBDE (38 *vs.* 28). Thirty-five of the 38 patients who underwent EP in group II were referred directly to gastroenterologists and had no surgical consultation prior to the procedure.

Table 1 characterizes the four groups according to age, number of comorbid illnesses, and percentage of patients presenting with acute biliary tract disease. For each patient, the number of comorbid illnesses was determined, and the number listed in Table 1 represents the arithmetic mean for each group. The number listed under acute illness represents the percentage of each group that presented with either acute cholecystitis, cholangitis, or pancreatitis. The mean age of patients in group I was significantly less than that of groups II and IV ($p < 0.05$). There were no differences, however, in the mean number of comorbid illnesses per group or the fraction that presented acutely ill.

Again, examining only patients in groups I and II over 70 years of age (Table 2), we found that those undergoing CBDE were still younger than those undergoing EP ($p < 0.05$). These groups were also similar with regard to

TABLE 1. *Group Characteristics*

Group	Age (yr) (Mean)	Age (yr) (Range)	No. of Comorbid Illnesses (Mean)	Acutely Ill (%)
I	58 ± 2*	19–88	1.2 ± 0.1	40
II	75 ± 2	25–104	1.7 ± 0.1	35
III	68 ± 6	50–84	1.0 ± 0.8	20
IV	68 ± 1	30–97	1.6 ± 0.1	23

* Group I *vs.* II and I *vs.* IV, $p < 0.05$.

TABLE 2. *Group Characteristics: Age >70 Years with Intact Gallbladder*

Group	Age (yr) (Mean)	Age (yr) (Range)	No. of Comorbid Illnesses (Mean)	Acutely Ill (%)
I	75 ± 1*	70–89	1.5 ± 0.2	36
II	84 ± 1	70–104	1.6 ± 0.2	42

* Group I *vs.* II, $p < 0.05$.

acute and chronic illnesses. Thus, EP was the preferred method of treating elderly patients with intact gallbladders, regardless of underlying health.

Length of hospitalization was greater for patients treated with CBDE than for those treated with EP ($p < 0.05$). Patients in group I were hospitalized 10.3 ± 0.6 days compared to 6.4 ± 0.8 for group II; group III patients spent 16.0 ± 4.8 days in the hospital compared to 6.0 ± 0.6 for group IV.

Technical success of the procedure was defined as clearance of all stones from the bile ducts. Retained stones constituted failure for the operative groups (groups I and III). Multiple endoscopic procedures were commonly necessary to achieve clearance in groups II and IV. Such cases were still considered technically successful if clearance was ultimately attained without need for operation. Table 3 lists the success rates for all groups. All five patients with retained stones after CBDE underwent percutaneous basket retrieval via the T tube tract without complication. Of the 23 patients who had unsuccessful attempts at EP, 18 underwent subsequent CBDE.

Table 4 depicts the complication rates for each group, and Table 5 lists the complications according to procedure (EP *vs.* CBDE). While the overall group complication rates did not differ significantly, the nature of the complications seemed more serious in patients undergoing EP. Sixteen of the 22 complications occurring in groups II and IV were directly a result of EP. There were six episodes of gastrointestinal (GI) hemorrhage (2 to 12 U), five duodenal perforations, four instances of biliary sepsis, and one case of pancreatitis. Seven of these 16 complications resulted in a need for operation (GI bleed, 3; duodenal perforation, 2; biliary sepsis, 2), which represented 4.7% of the total number of patients who underwent EP. In contrast to the EP complications, five of the 13 CBDE complications were directly a result of the procedure. Two of these complications (hemorrhage and pancreatitis) necessitated reoperation, representing 2.5% of all patients undergoing CBDE.

TABLE 3. *Technical Success Rate*

Group	N	Failures	Success Rate (%)	Subsequent Procedures (N)
I (CBDE)	76	4	95	Basket extraction (4)
II (EP)	54	6	89	CBDE (3)
III (CBDE)	5	1	80	Basket extraction (1)
IV (EP)	102	17	85	CBDE (15)

TABLE 4. *Complication Rate*

Group (N)	Complications (%)
I (76)	11 (14)
II (54)	5 (9)
III (5)	2 (40)
IV (102)	17 (16)

Seven of the 237 admissions for choledocholithiasis ended in hospital death. These seven patients are characterized in Table 6. The youngest patient who died was 70 years old. Each patient's group assignment reflects the initial procedure performed at VMMC. Only one patient had CBDE as the initial procedure. Four of the seven patients eventually required both EP and CBDE. One patient had undergone cholecystectomy and CBDE elsewhere and was transferred ten days postoperatively for endoscopic retrieval of a retained stone. Three patients underwent EP, then subsequently required operation for continued symptoms, technical failure, or complications. Myocardial infarction and sepsis were the most frequent causes of death.

The overall mortality rate was 3.0%, 5.8% for patients 70 years or older, and 0% for patients less than 70 (Table 7). Mortality rates were similar for all groups.

Cox's logistic regression method indicated that three factors increased the risk of death: presence of complications, age of 70 years or older, and technical failure. The following factors did not independently increase the risk of mortality: number of comorbid illnesses, type of procedure initially attempted, and presentation with acute biliary tract conditions.

Follow-up data were obtained for 34 of 48 patients (72%) who had successful EP with intact gallbladders. The mean length of follow-up was 28 months. Seven of these patients (21%) underwent subsequent cholecystectomy for either acute cholecystitis or chronic continued symptoms. One patient underwent laparotomy elsewhere and was found to have chronic pancreatitis. Her gallbladder was not removed. One patient had two separate episodes of CBD stones during the study period and was treated twice with EP. Another patient had her first EP in 1980 before the study period and had her second EP in 1984 for another episode of stones.

TABLE 5. *Complications*

Groups I and III (CBDE)	Groups II and IV (EP)
Procedure-related	
Biliary sepsis 3	GI hemorrhage 6
Pancreatitis 1	Duodenal perforation 5
Hemobilia 1	Biliary sepsis 4
	Pancreatitis 1
Subtotal 5 (6%)	Subtotal 16 (10%)
Not procedure-related	
Respiratory 3	Acute MI 2
Urinary tract 3	Acture renal failure 1
Miscellaneous 2	Miscellaneous 3
Subtotal 8 (10%)	Subtotal 6 (4%)
Total 13 (16%)	Total 22 (14%)

TABLE 6. *Characteristics of Patients Who Died*

Patient No.	Age	Group	Procedures	Acutely Ill	Cause of Death
1	83	I	CBDE	+	Sepsis
2	93	II	EP	−	Sepsis
3	89	IV	EP	+	Sepsis
4	75	II	EP, CBDE	−	MI
5	74	IV	EP, CBDE	−	GI bleed
6	70	IV	EP, CBDE	−	Sepsis
7	87	IV	CBDE, EP	−	MI

Discussion

In examining the recent management of choledocholithiasis at VMMC, we found that the overwhelming majority of patients with CBD stones after cholecystectomy were treated with EP. This was not surprising, in view of VMMC's regional reputation for skilled endoscopy and the current trend in both Europe and the United States to treat recurrent stones in this manner.[8,12,13] During the past 5½ years, however, 41% of all patients with gallbladders intact, and 58% of patients over 70 years of age with gallbladders intact, were initially treated with EP. While the patients who underwent EP were significantly older than those undergoing CBDE, they were similar with regard to both chronic comorbidity and the fraction that presented acutely ill. Thus, at our institution, EP has become the preferred method of treating elderly patients with CBD stones and gallbladders intact, regardless of underlying health. This unexpected preference reflects the current thinking of general physicians and gastroenterologists since 92% of these elderly patients underwent EP without prior surgical consultation.

Can this radical shift in management be justified on the basis of improved results? The technical success rates of EP and CBDE were similar, and compared favorably with those reported by other institutions.[14,20,22] While the overall complication rates were also similar, we found that the actual complications of EP were more frequently life-threatening and were most often a direct result of the procedure (GI hemorrhage, duodenal perforation, biliary sepsis). Nearly half of these EP-related complications necessitated a subsequent, often urgent operation. The overall complication rate of 14% associated with EP may seem high when compared to other reports. Most studies on EP have reported only the procedure-related complications,[8,9,14,23] thus lowering the published rates and making comparison to surgical series somewhat imbalanced. In addition, one of these reports[14] noted a complication rate of 13% when cases were reviewed by an independent observer, as in the current study. Mortality rates of all groups were also similar and may seem high for EP and low for CBDE. This may be explained by two factors. First, four of the seven patients who died required both EP and CBDE, making it difficult to attribute the death to one procedure or the other. Second, the patients who underwent EP were older than those who underwent CBDE, making comparison between the groups less valid. Several series have recently been published that examine the results of CBDE before EP was widely utilized, and thus before it exerted any such selection bias. Pitt et al.[24] reported no deaths in 47 patients undergoing cholecystectomy and CBDE; Broughan et al.[13] reported a 0.8% mortality rate for operation on patients with recurrent stones only; McSherry and Glenn[25] reviewing 30 years experience, reported a mortality rate of 3.2% for all patients undergoing CBDE. Others document similar mortality rates.[26] Our mortality rate of 3.0% is within this range. These data suggest that CBDE can be performed with morbidity and mortality rates at least equal to those currently observed for EP, and that the widespread use of EP at our institution has not reduced the overall mortality of CBD stones.

Recognizing the limitations of retrospective studies, we subjected our data to multivariate analysis, and

TABLE 7. *30-Day Mortality Rates*

Group	Deaths (%)	Deaths (%) Patients >70 Years
I	1 (1.3)	1 (3.6)
II	2 (3.7)	2 (5.3)
III	0	0
IV	4 (3.9)	4 (7.5)
Total	3.0	5.8

found that, indeed, type of procedure performed was not an important determinant of mortality rate. Rather, age greater than 70 years, technical failure, and presence of complications significantly increased the risk of death. Although four of the seven patients who died eventually required both EP and CBDE, the need for a second procedure did not independently increase risk when adjusted for technical failure. Numerous studies have documented age as a risk factor for benign biliary tract procedures.[10,24,25,27] This has generally been attributed to the greater proportion of elderly patients who require emergent procedures and to concurrent chronic illness.[26,28] Our data, however, do not support these notions. We did not find that acute cholecystitis, pancreatitis, or cholangitis negatively affected survival. In addition, the risk of mortality did not increase in proportion to the number of comorbid conditions, and age remained a significant risk factor even when adjusted for chronic disease. Thus, the elderly patient remains fragile with regard to biliary tract procedures, regardless of underlying health. Whichever procedure is chosen should be performed successfully and without complication.

Of the patients undergoing EP with intact gallbladders, 21% required subsequent cholecystectomy. The cholecystectomy rates reported by other institutions range from 8.6%–28%.[14,23,29,30] Siegel et al.[30] recently reported that 109 of 1272 patients (9%) who underwent EP with gallbladders intact developed acute cholecystitis within 10 days of the procedure. The majority of these patients responded to medical management, but 25 required operation. Eight of the patients who required emergent operation died. This suggests that acute cholecystitis should also be considered a frequent and potentially fatal complication of EP in patients with intact gallbladders. Endoscopists have reasoned that EP spares the need for CBDE even if cholecystectomy becomes necessary, and thus should reduce the morbidity and mortality rates of operation. Neoptolemos et al.[31] recently tested this theory with a prospective study. Patients were randomly assigned to undergo either cholecystectomy with CBDE or EP followed by cholecystectomy 3 days later. The complication and death rates were nearly doubled for the latter group, although the study was halted before the differences became statistically significant. This implies that the risks for the two procedures (EP and cholecystectomy) are additive and that the risk of EP in these patients was at least as great as the risk of CBDE.

In 1980 McSherry and Glenn stated that "the mortality rates of secondary choledochotomy and endoscopic papillotomy are comparable and that . . . acceptance of [EP] on the basis of less mortality and morbidity in comparison to surgical therapy is unjustified."[25] Our data confirm this opinion. We believe, however, that EP should remain the procedure of choice for CBD stones after cholecystectomy. While use of EP is not justified on the basis of improved results, it does permit less in-hospital time, which implies greater cost-effectiveness and patient satisfaction. The role of EP alone as the initial therapy for patients with intact gallbladders, however, is not yet clearly established. Although cholecystectomy may be avoided in 75–80% of these patients, this benefit must be weighed against the excessive mortality risk that accompanies complicated unsuccessful procedures ending in emergent operation. Studies suggest that certain subsets of patients with intact gallbladders might benefit from early EP, such as those with cholangitis[32] or pancreatitis.[33] These groups remain to be defined by controlled, prospective studies.

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Reoperation for Congenital Choledochal Cyst

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A reoperation after excisional procedure was carried out in seven cases due to early or late postoperative complications. Of the 12 patients with early complications, four underwent relaparotomy due to anastomotic leakage and bleeding. Late complications were seen in nine patients with recurrent cholangitis caused by an anastomotic stricture, and three patients with intrahepatic involvement required a reoperation several years after the initial surgery. Recurrent cholangitis after biliary reconstruction mainly occurs due to an anastomotic stricture of the hepaticoenterostomy. There was no significant difference in the results between hepaticoduodenostomy and hepaticojejunostomy over a long follow-up period. A wide anastomotic stoma that permits free drainage of bile into the intestine is imperative to the prevention of cholangitis, and can be created by an incision extending along the lateral wall of both the hepatic ducts with a hepaticoenterostomy at the hilum. This procedure is obviously necessary in all patients with or without intrahepatic involvement. Carcinoma of the intrahepatic ducts and the retained distal choledochus have rarely developed in patients undergoing cyst excision followed by biliary reconstruction. Complete excision of the whole extrahepatic bile duct could prevent carcinoma arising in the distal choledochus, although it could not prevent carcinoma arising from the intrahepatic ducts. However, patients with carcinoma of the intrahepatic duct were reported to have had symptoms of biliary stricture for a long time since the cyst excision. Bile stagnation in the intrahepatic ducts is possibly responsible for the development of carcinoma. A wide anastomosis resulting in free drainage of bile appears to be essential to the prevention of carcinoma arising in the intrahepatic ducts after cyst excision.

SURGICAL TREATMENT of choledochal cyst has changed recently. Enteric drainage procedures, cystoduodenostomy, and cystojejunostomy have been abandoned due to high morbidity rates and the potential danger of carcinoma development in the cyst wall; cyst excision followed by biliary reconstruction is gaining recognition as the treatment of choice.[1-4] Moreover, excision interrupts an anomalous pancreatobiliary ductal union that is commonly observed in choledochal cysts and results in hazardous effects to the biliary epithelium due to refluxing of pancreatic juice.[5] The cyst excision, however, has led to several early and late postoperative complications. Of 92 patients who underwent various procedures at the Okayama University Hospital and the Hospital of Kagawa Medical School, 23 patients who underwent reoperation are reviewed in this article.

Clinical Data

Between 1960 to 1986, 92 patients with choledochal cyst underwent various procedures without operative mortality at our clinics. Cysts were classified by our classification[4]: type Ia, cystic dilatation (21 patients), type Ic, diffuse dilatation (18), type III, choledochocele (1), and type IV-A, intrahepatic involvement (52) patients. Eight patients died of carcinoma arising in the cyst soon after surgery.[6] Five of these patients had primary, and three had secondary carcinoma, which developed several years after enteric drainage. In the remaining 84 patients without carcinoma, primary excision of the cyst was performed in 60, and secondary excision converted from various drainages was done in 13 patients. A total of 73 patients finally underwent excisional procedures with biliary reconstruction: hepaticoduodenostomy in 51, hepaticojejunostomy Roux-en-Y in 20, pancreatoduodenectomy in 1, and excision of choledochocele in 1. The 11 patients who were treated prior to 1967 still have enteric drainage and have been lost to follow-up study. Of the 73 with cyst excision, seven patients underwent a relaparotomy due to several postoperative

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complications. In total, 23 patients of reoperation for choledochal cyst were analyzed.

TABLE 1. *Reoperation of Choledochal Cyst*

	Reoperation			
Former Operation	Ex and H-D	Ex and H-J	Palliative Operation	Total
Cholecystostomy	4	3	—	7
Choledochostomy	—	1	—	1
Cystoduodenostomy	3	1	2	6
Cystojejunostomy Roux-en-Y	—	1	1	2
Cyst excision	5	2	—	7
Total	12	8	3	23

Palliative operation was carried out in three patients with carcinoma.

Ex = cyst excision, H-D = hepaticoduodenostomy, H-J = hepaticojejunostomy Roux-en-Y.

Results

Reoperation was performed in 23 patients, 8 of whom had external drainage, 8 of whom had enteric drainages (including 3 who developed carcinoma), and 7 of whom underwent excisional procedures (Table 1). The reoperation rate in the 84 patients without carcinoma was 14.3% (12/84), excluding the 8 patients with external drainage.

Reoperation in Cases of External Drainage

All eight patients with external drainage underwent secondary excisional procedures with favorable results. Seven of these patients underwent cholecystostomy primarily due to severe cholangitis in 4, acute pancreatitis in 1, and bile peritonitis in 2. The remaining patient underwent cholecystectomy with T tube choledochostomy, and hepaticojejunostomy Roux-en-Y at the hepatic hilum with end-to-end anastomosis was performed secondarily after removal of the whole extrahepatic bile duct because of an anomalous pancreatobiliary ductal union that was identified with tube-cholangiograms.

Reoperation in Cases of Enteric Drainage

Of the 19 patients with enteric drainage, 5 patients underwent secondary excision of the cyst due to recurrent cholangitis with abdominal pain and high fever occurring several years after surgery and 3 patients ended up with palliative operation due to carcinoma that developed in the retained cyst (Table 2). The remaining 11 patients with enteric drainage were experienced prior to 1967 and have been lost to follow-up study.

Reoperation in Cases of Excisional Procedure

An excisional procedure was performed in 73 patients, of whom 21 patients had postoperative complications: early in 12 and late in nine. A reoperation, however, was carried out in only seven patients.

The early complications generally could be managed conservatively with favorable results (Table 3). Only four patients underwent a reoperation due to anastomotic leakage and postoperative bleeding. Of two patients with anastomotic leakage, one underwent a conversion from a hepaticocholedochostomy to a hepaticojejunostomy Roux-en-Y on the 11th postoperative day, and the other underwent a relaparotomy due to unsuitable drainage of bile caused by kinking of the silastic drain near the anastomotic site. Postoperative bleeding developed in two patients. One had massive bleeding from the dissected layers around the pancreatic head on the day of the operation, and several pursestring sutures around the bleeding site were effective. The other patient had bleeding from the site of hepaticoduodenostomy, which was converted into a hepaticojejunostomy Roux-en-Y after closing of the duodenal stoma.

Late complications occurred due to recurrent ascending cholangitis caused by anastomotic stricture. Several attacks of cholangitis with abdominal pain and high

TABLE 2. *Case Summary of Reoperation in Enteric Drainage Patients*

Age (yr)	Sex	Type	Enteric drainage	Complications	Reoperation	Follow-up
12	F	IV-A	C-D at 7 mo	Cholangitis, stones	Ex, H-D at hilum	10 mo Good
13	M	IV-A	C-D at 3 yr	Cholangitis, stones	Ex, H-D at hilum	13 yr Good
18	M	IV-A	C-D at 17 yr	Cholangitis	Ex, H-D at hilum	12 yr Good
23	F	Ia	C-D at 16 yr	Cholangitis	Ex, H-J at hilum	17 yr Good
26	F	Ia	C-J at 14 yr	Cholangitis	Ex, H-J at hilum	4 yr Good
19	F	Ia	C-D at 17 yr	Squamous cell carcinoma	Simple laparotomy	10 d Died
26	M	IV-A	C-D at 22 yr	Adenocarcinoma, liver metastasis	Intrahepatic C-J	2 mo Died
26	F	IV-A	C-J at 17 yr	Adenocarcinoma	Palliative Ex, H-J	1 mo Died

C-D = cystoduodenostomy, C-J = cystojejunostomy Roux-en-Y, Ex = cyst excision, H-D = hepaticoduodenostomy, H-J = hepaticojejunostomy Roux-en-Y.

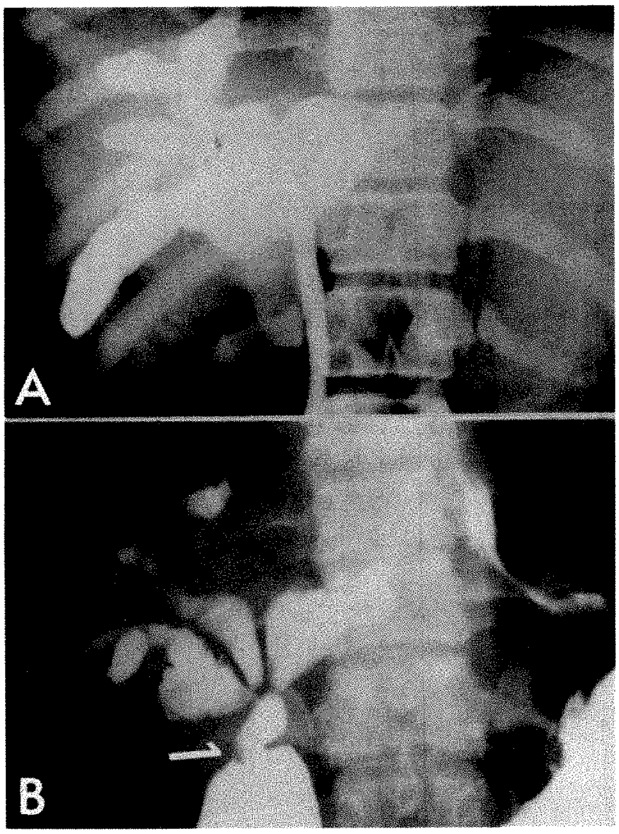
TABLE 3. *Postoperative Complications after Excisional Procedure*

Complications	Ex, H-D at Hilum	Ex, H-J at Hilum	Total
Leakage	3 (2)	—	3 (2)
Bleeding	1	2 (2)	3 (2)
GI bleeding	—	1	1
Acute pancreatitis	2	—	2
Pancreatic fistula	1	—	1
Intestinal obstruction	1	1	2
Subtotal	8 (2)	4 (2)	12 (4)
Cholangitis	5 (2)	4 (1)	9 (3)
Total	13 (4)	8 (3)	21 (7)

The parentheses show the number of patients undergoing reoperation.

Ex = cyst excision, H-D = hepaticoduodenostomy, H-J = hepaticojejunostomy Roux-en-Y.

fever were observed in nine patients (12.3%). The cholangitis usually responded to antibiotics and resulted in no demonstrable hepatic dysfunction subsequently. Of these nine patients, five patients underwent hepaticoduodenostomy and four underwent hepaticojejunostomy Roux-en-Y. Seven patients had a type IV-A cyst (intrahepatic involvement). Only three patients with intrahepatic involvement, however, required a reoperation several years after excisional procedures.



FIGS. 1A and B. Case 1. *A*. Operative cholangiogram at the age of 11 shows dilatation of the intrahepatic ducts near the hilum. *B*. Cholangiogram at the age of 18 shows cloverlike strictures on the confluence of both the hepatic ducts. The arrow indicates the anastomosis of the hepaticoduodenostomy below the hilum.

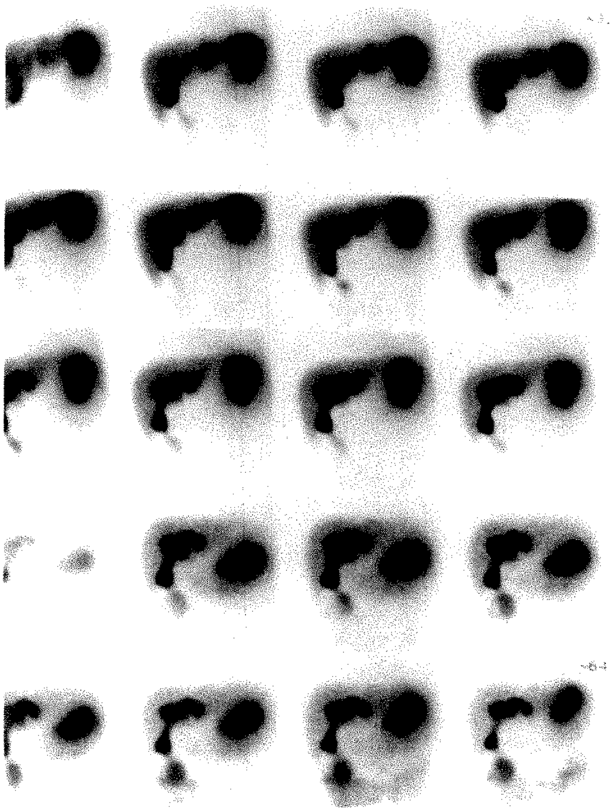


FIG. 2. Case 2. Scintigrams delineate well the intrahepatic ducts near the hilum and the jejunal interposition even at 60 minutes after injection of ^{99m}Tc HIDA, and suggest strictures of both the hepaticojejunal and jejunojejunal anastomoses.

Case Reports

Case 1

The patient had undergone cyst excision with hepaticoduodenostomy below the hepatic hilum at the age of 11 years.[7] She had occasionally complained of abdominal pain and fever beginning 2 years after surgery. At the age of 18, strictures of the confluence of the bilateral hepatic ducts were revealed by endoscopy and barium study (Fig. 1). The hepaticoduodenostomy was converted to a hepaticojejunostomy Roux-en-Y at the hilum with end-to-end anastomosis after plasty of both the hepatic ducts. She is now 29 years old without any symptoms.

Case 2

A 2-year-old boy underwent a cyst excision elsewhere followed by hepaticojejunostomy with jejunal interposition (22 cm in length) performed distal to the hilum with end-to-side anastomosis. However, he complained of intermittent abdominal pain and fever several months after surgery. At the age of 6, scintigraphy using ^{99m}Tc HIDA suggested an anastomotic stricture, which was confirmed with operative cholangiograms (Fig. 2). A relaparotomy revealed intrahepatic biliary calculi and slight stricture of the jejunojejunal anastomosis with dilatation of the jejunal blind pouch (Fig. 3). The hepaticojejunostomy was changed to a hepaticoduodenostomy at the hilum. He has been free of symptoms for 12 months since the second surgery.

Case 3

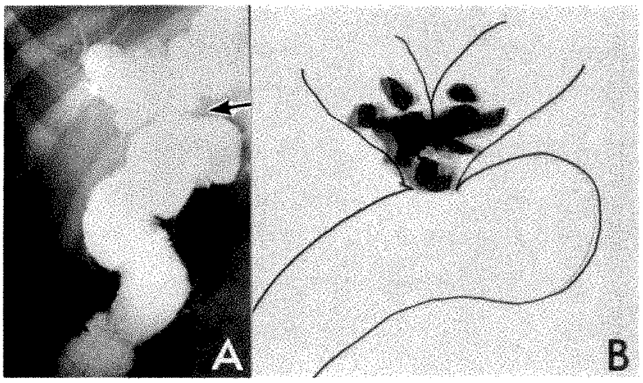
A 5-year-old girl underwent an excisional procedure with hepaticoduodenostomy below the hilum due to diffuse dilatation of the extrahepatic bile duct with bilateral intrahepatic involvement (Fig. 4). Severe abdominal pain with high fever occasionally developed since the age of 11 years. At the age of 12, a gastrointestinal tract examination with barium showed no demonstrable biliary tree, suggesting an anastomotic stricture. Endoscopy and ^{99m}Tc HIDA scintigraphy revealed a stricture of the anastomotic stoma with highly dilated intrahepatic ducts containing numerous biliary stones. After left hepatectomy and complete removal of biliary calculi in the right lobe, the hepaticoduodenostomy was released, and a wide anastomosis between the right intrahepatic duct and Roux-en-Y jejunum was performed. She has remained well for 4 months since surgery.

Discussion

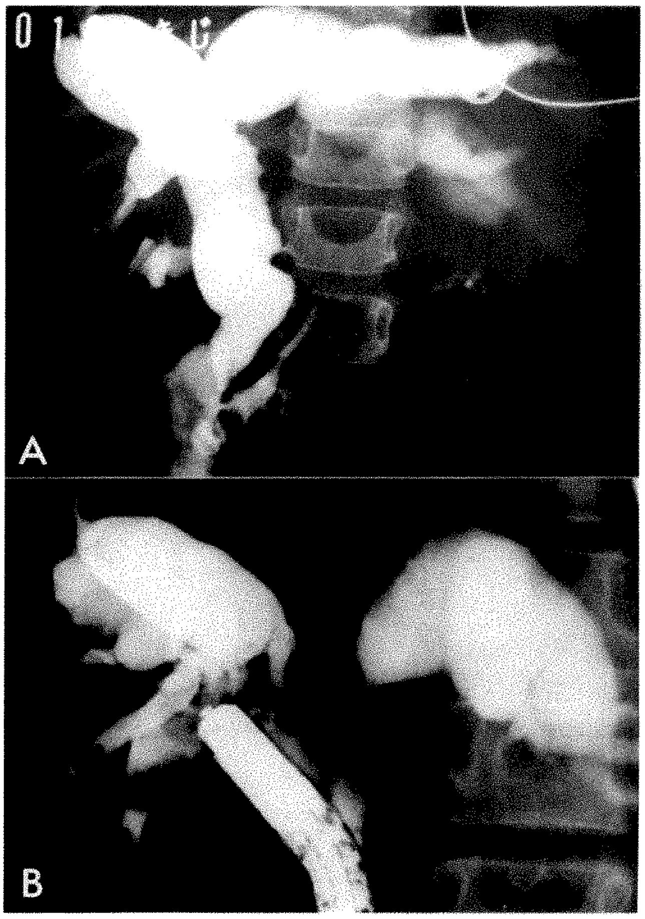
External drainage is usually carried out on patients in poor general condition, resulting from septicemia due to cholangitis, acute pancreatitis, biliary perforation, or hepatic dysfunction with jaundice, and excisional procedure can be performed without any difficulty within a few months after the surgery. If an enteric drainage was performed when the patient is in poor condition, the patient might hesitate to undergo a definitive operation due to transitory improvement of complaints. Cholecystostomy is recommended as a drainage procedure because of its simplicity and usefulness as a guide for dissection of the cyst.

Recurrent cholangitis, anastomotic stricture with jaundice, biliary calculi, and carcinoma in the cyst tend to occur after enteric drainage, and correction surgery is frequently necessary (Table 4).[3,6,8–14] The risk of developing carcinoma in the retained cyst appears to be 50%,[9] and the mean age at detection of carcinoma is 35 years of age, 15 years younger than that of primary carcinoma. The prognosis is very dismal, and all patients with enteric drainage die soon after the detection of carcinoma.[6] The development of carcinoma is possibly caused by regurgitation of pancreatic juice into the choledochus through an anomalous pancreatobiliary union that is usually observed in choledochal cyst. Enteric drainage leaves a malunion and cannot interrupt refluxing of pancreatic juice. Therefore, it should be abandoned and converted early to excisional procedure, even if the patient has no complaints. A secondary excision is easier than previously thought. Blunt dissection of the inner layer of the shrunken cyst can avoid injury to the hepatic artery and portal vein by leaving the outer layer intact.[2,15]

An excisional procedure with biliary reconstruction is the treatment of choice in terms of preventing malignant complications and interrupting a malunion. Morbidity and mortality rates with cyst excision are seldom seen due to recent advances in operative techniques and postoperative management.[1,2,10,12,16] However, early and



FIGS. 3A and B. Case 2. *A*. Operative cholangiogram at the age of 6 shows a stenosis of the hepaticojejunostomy (arrow) with dilatation of the intrahepatic ducts and jejunal blind pouch. *B*. Biliary calculi are seen in the hepatic ducts just above the anastomosis.



FIGS. 4A and B. Case 3. *A*. Operative cholangiogram at the age of 5 shows diffuse dilatation of the intrahepatic and extrahepatic ducts with pancreatobiliary malunion. *B*. Cholangiogram 7 years after hepaticoduodenostomy below the hepatic hilum shows cystic dilatation of the intrahepatic ducts.

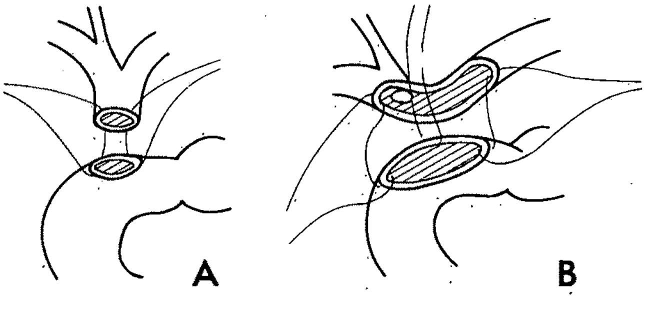
TABLE 4. *Reoperation Rate of Enteric Drainage*

Authors	Year	No. of Patients*	%
Flanigan[9]	1975	47/158	29.7
Yamaguchi[10]	1980	63/401	15.7
Powell et al.[3]	1981	20/91	22.0
Miyano et al.[19]	1984	9/15	60.0
Takiff et al.[11]	1985	12/23	52.2
Deziel et al.[12]	1986	14/16	87.5

* Denominator, no. of patients with enteric drainage; numerator, no. of patients undergoing reoperation.

late complications of excisional procedures have occasionally been reported.[9,11,12,14]

Early complications include an anastomotic leakage, bleeding from the dissected outer layer or gastrointestinal tracts, acute pancreatitis, pancreatic fistula, and intestinal obstruction. Minor leakage can be managed effectively by long-term drainage. However, hepaticocholedochostomy, so-called anatomical reconstruction, is inappropriate for choledochal cyst, even if leakage does not occur[14,17] due to leaving a pancreatobiliary malunion that causes the refluxing of pancreatic juice. Bleeding from the dissected layer of the cyst can be prevented with electrocoagulation or pursestring sutures. Gastrointestinal bleeding due to a peptic ulcer might occur in patients with hepaticojejunostomy,[18] and could be treated with H2 blockers. Acute pancreatitis and pancreatic fistula[12] may be caused by dissecting the terminal bile duct, which is connected with the pancreatic duct in the pancreatic head. These problems can usually be managed conservatively. Intestinal obstruction would be expected to develop more often in hepaticojejunostomy Roux-en-Y patients than in hepaticoduodenostomy patients because of the necessity to manipulate the abdominal cavity below the transverse mesocolon in the former. Hepaticoduodenostomy at the hilum, however, is prone to cause a transient duodenal obstruction due to kinking of the duodenum caused by lifting it up to the hepatic hilum after extended kocherization. Most of these obstructions tend to be managed successfully by nasogastric drainage with fasting for several days. A duodenal obstruction due to compression by the jejunal limb after a hepaticojejunostomy Roux-en-Y has been reported to be an unusual complication that requires correction surgery.[19]



FIGS. 5A and B. *A.* Hepaticoduodenostomy below the hilum. *B.* Hepaticoduodenostomy at the hilum with a wide stoma created by an incision along the lateral wall of the hepatic ducts.

Existence of late complications is very important in evaluation of a surgical procedure. Cholangitis, biliary calculi, and carcinoma have been occasionally observed in long-term follow-up studies after excisional procedures, and have become the object of reoperations.[10]

Recurrent cholangitis with severe abdominal pain, high fever, and biliary calculi after biliary reconstruction is a serious complication. It mainly occurs due to biliary stasis caused by an anastomotic stricture of hepaticoenterostomy, particularly in patients with intrahepatic involvement. Biliary stasis also develops from a stricture of the jejunojejunal anastomosis in the Roux-en-Y jejunum or the jejunoduodenal anastomosis in hepaticoduodenostomy with jejunal interposition, and from compression of a jejunal limb with the preduodenal portal vein.[19] No significant difference was found in the results between hepaticoduodenostomy and hepaticojejunostomy Roux-en-Y over a long follow-up period. A wide anastomotic stoma, which permits free drainage of bile juice into the intestine, may be imperative to the prevention of cholangitis.[2,15] A wide anastomosis cannot be produced in an anastomosis between the common hepatic duct and the intestine because the common hepatic duct is relatively small and commonly had a denuded mucosa with marked fibrosis that resulted in a stenosis. A wide stoma can be created by an incision extending along the lateral wall of both the transected hepatic ducts, and then hepaticoenterostomy is performed at the hilum (Fig. 5). This procedure is obviously necessary in all patients with or without intrahepatic involvement. In the Roux-en-Y procedure, an end-to-side anastomosis with blind pouch formation, which might be performed to adapt the size of the common hepatic duct, should not be carried out. An end-to-end anastomosis with plasty of both the hepatic ducts to fit with the jejunal stoma is recommended. Moreover, anastomosis with cyst remnants leaving after excision to get a sufficiently large stoma is also probably unsuitable because of leaving the mucosa prone to malignant change.

Carcinoma of the intrahepatic ducts and the distal choledochus developed in 12 patients who underwent an apparently insufficient cyst excision followed by biliary reconstruction (Table 5).[20-23] Complete excision of the extrahepatic bile duct from the hilum to the pancreatobiliary junction could prevent carcinoma arising in the distal choledochus retained after insufficient excision,[6,12,23] while it could not prevent carcinoma arising from the intrahepatic ducts. However, the four reported

TABLE 5. *Carcinoma Developing after Excisional Procedure*

Author	Year	Age at Ex (yr)	Sex	Age When Cancer Identified (yr)	Site of Carcinoma	Operation for Carcinoma	Type	Remarks
Thistlethwaite and Horwitz[20]	1967	21	M	23	Anastomotic site	Drainage	Ia	Undifferentiated carcinoma
Gallagher et al.[21]	1972	51	F	58	Intrahepatic duct	None	IV-A	Adenocarcinoma
Terauchi[24]	1978	11	M	26	Intrahepatic duct	Intrahepatic C-J	IV-A	Adenocarcinoma
Chaudhuri et al.[22]	1982	21	F	38	Intrahepatic duct	Reexcision	IV-A	Adenocarcinoma
Uchimura[25]	1982	24	F	28	Intrahepatic duct	Pancreatoduodenectomy	Ia	Missing carcinoma at cyst excision
Kaneta[26]	1984	47	F	54	Intrahepatic duct	Drainage	Ia	Multiple calculi
Miyoshi[27]	1984	20	F	29	Terminal duct	Drainage	Ia	Insufficient Ex
Kure[28]	1984	35	M	39	Intrahepatic duct	Laparotomy	IV-A	Adenocarcinoma
Egami[29]	1985	17	F	23	Terminal duct	Laparotomy	Ia	Insufficient Ex
Yoshikawa et al.[23]	1986	14	F	27	Terminal duct	Pancreatoduodenectomy	IV-A	Insufficient Ex
Deziel et al.[12]	1986	?	?	?	Intrahepatic cyst	?	IV-A	Adenocarcinoma
		?	?	?	Terminal duct	?	IV-A	Insufficient Ex

Ex = cyst excision, C-J = cystojejunostomy Roux-en-Y.

cases of carcinoma of the intrahepatic duct had symptoms of biliary stricture for a long time from the time the cyst was excised until the carcinoma was detected.[12,21,22] Long-lasting bile stagnation in the intrahepatic ducts is possibly responsible for the development of carcinoma. A wide anastomotic stoma yielding free drainage of bile after cyst excision is probably essential to the prevention of carcinoma arising in the intrahepatic biliary tree.

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Risk Factors in Relation to Postoperative Complications in Patients Undergoing Esophagectomy or Gastrectomy for Cancer

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To clarify the risk factors contributing to postoperative complications in the elderly patients (over 70 years) undergoing esophagectomy and/or gastrectomy, 364 patients with primary cancer seen were evaluated. As a result, some characteristic patterns of stress response in the elderly could be detected as follows: the disorders of the vital organs were more important indices for the development of postoperative complications rather than age, and a reduction in the maximum response of the stress hormones to surgical procedures in aged patients was noted; moreover, the functional variability of target organ in the aged group was confirmed. Studies on the hormonal response to surgery suggest that the restriction of fluid replacement is advisable until the third postoperative day, maintaining the host on the dry side, to prevent cardiopulmonary complications. As the nutritional status in the patients with esophageal and gastric cancer goes from bad to worse with the advancing clinical stages, adequate perioperative nutrition is imperative to prevent complications such as anastomotic leakage, wound dehiscence, and/or infections. For the treatment of anastomotic leaks after esophagectomy and esophagogastrectomy, more than 45 kcal/kg/d must be provided, and the serum albumin level must be restored to 3.5 g/dL in order to achieve spontaneous healing of small anastomotic leakages.

DESPITE IMPROVEMENTS in preoperative evaluation, operative techniques, and postoperative care, esophageal resection and reconstruction through a combined thoracoabdominal procedure for the patients with esophageal and/or proximal gastric cancer still remains a formidable operation in patients whose nutritional and pulmonary status have been compromised by impaired swallowing.[1]

Since esophagectomy or esophagogastrectomy is associated with a high rate of complications, mainly pulmonary complications and anastomotic leakage, a preoperative assessment of cardiopulmonary function and nutritional status is thought to be mandatory.[2] Besides, esophagectomy and/or esophagogastrectomy with thoracotomy elicit a maximal the stress response especially in elderly patients with cancer of the esophagus and/or proximal stomach.

Since the functional reserve of various organs is decreased in elderly patients, the selection of the most suitable surgical procedure and the assessment of each patient's tolerance for surgical stress are difficult to determine. In recent years, aggressive nutritional support and proper nutritional assessment during the perioperative period have become essential in achieving a satisfactory recovery because the operations for esophageal and gastric cancer have become more radical and more extensive.[3,4] It is also imperative to clarify the relationship between anastomotic leaks and the nutritional status in these cancer patients.

The present study was designed to analyze the significant risk factors that could contribute to postoperative complications following esophagectomy or esophagogastrectomy, and to investigate the characteristic pattern of stress response to surgery for primary cancer of the esophagus and/or proximal stomach in patients over 70 years old.

Materials and Methods

During the 6-year period from 1980 through 1985, there were 364 patients with primary cancers of the esophagus and stomach who underwent esophagectomy, esophagogastrectomy, and/or partial gastrectomy

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TABLE 1. *Comparison Between Aged and Control Group of Patients with Esophageal or Esophagocardial Carcinoma with Respect to Preoperative Organ Impairment*

	Aged Group (N = 89)	Control Group (N = 275)
Impaired cardial function*	44 (49%)	62 (22%)
Impaired pulmonary function*	36 (40%)	32 (12%)
Impaired liver function	6 (7%)	21 (8%)
Impaired renal function*	13 (15%)	9 (3%)
Impaired nutritional status	31 (35%)	74 (27%)
Others	15 (17%)	20 (7%)
Total	145 (163%)	218 (79%)

* Statistically significant by chi-square test ($p < 0.005$).

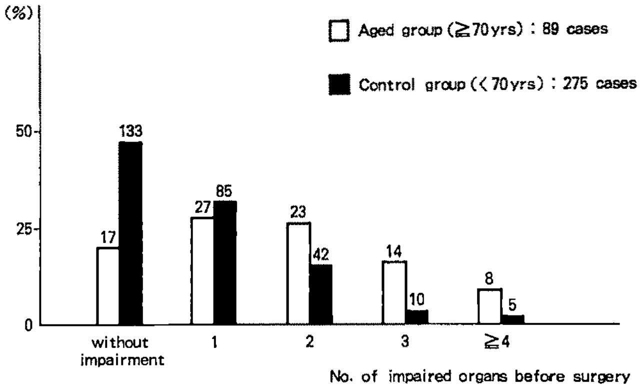

FIG. 1. Comparison between aged and control patients with respect to impaired organ function seen before surgery.

in our clinic. Of these 364 patients, the last 22 were analyzed with regard to their stress hormone responses and functional changes in the major vital organs in response to surgical stress. There were 19 men and 3 women, ranging in age from 43 to 78 years old, with an average age of 63.4 years. The 22 patients were separated by age into two groups consisting of equal numbers of patients. Eleven of them were over 70 years old and the other 11 patients were under 70 years old.

All of the patients with cancer of esophagus and/or cardia underwent either total or partial resection of the esophagus, through a right or left thoracoabdominal approach, with reconstruction using a stomach tube or a portion of the colon as a substitute placed via the posterior mediastinal route or retrosternal route.

The levels of renin (R), aldosterone (Ald), antidiuretic hormone (ADH), epinephrine (E), and norepinephrine (NE) were measured at 14 specified times during the perioperative period (within 10 days after surgery). Blood catecholamines were measured by the HPLC-THI method,[5] and the remainder were measured by radioimmunoassay methods.[6-8]

For perioperative nutritional assessments, 34 patients with esophageal cancer at different stages were analyzed. Changes in the actual body weight as a percentage of the ideal body weight (%IBW) were calculated. As an index of body habitus, tricep skinfold thickness (TSF) and arm muscle circumference (AMC) were measured by the method of Blackburn et al.[9] Sixty-two patients admitted for cholecystectomy were also investigated as controls. They were otherwise healthy and had normal liver function tests on admission to the hospital. All of the other clinical data were obtained by routine methods in our clinical laboratory. The diagnoses of anastomotic leakage and pulmonary complications were confirmed on clinical data and radiologic findings. Pulmonary complications were documented by location (right or left) and type (atelectasis, pulmonary edema, bronchopneumonia, and other pulmonary abnormalities).

Results

Of 364 patients with primary esophageal and/or gastric cancer, 89 (24%) were over 70 years old. With respect to risk factors, of the 89 patients in the elderly group, 72 (81%) showed some impairment of vital organs preoperatively, whereas of 275 patients under 70 years old, only 142 (52%) had such a preoperative impairment. There were significant differences between the older group and the control group with regard to the preoperative impairment of cardiac, pulmonary, and renal function ($p < 0.005$) (Table 1). In addition, the

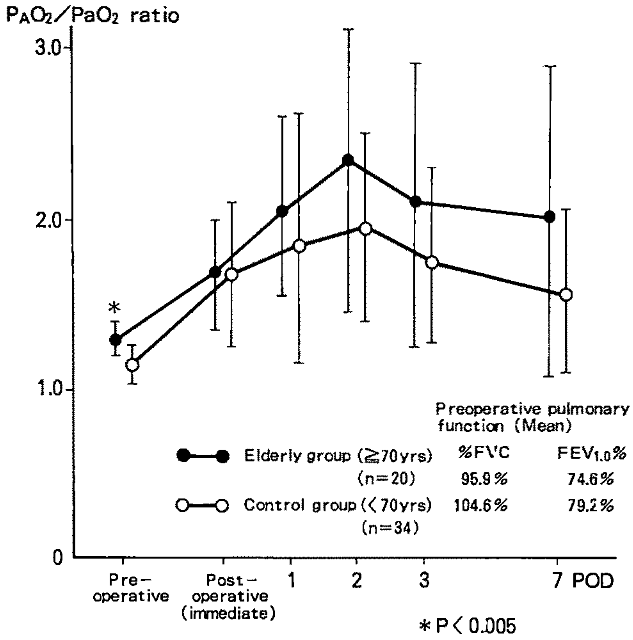

FIG. 2. Comparison between aged and control groups with respect to the perioperative change of oxygenation in patients undergoing esophagectomy or esophagogastrectomy for cancer. Results are given as mean ± SD. *Significant difference between two groups by Student's t-test ($p < 0.005$).

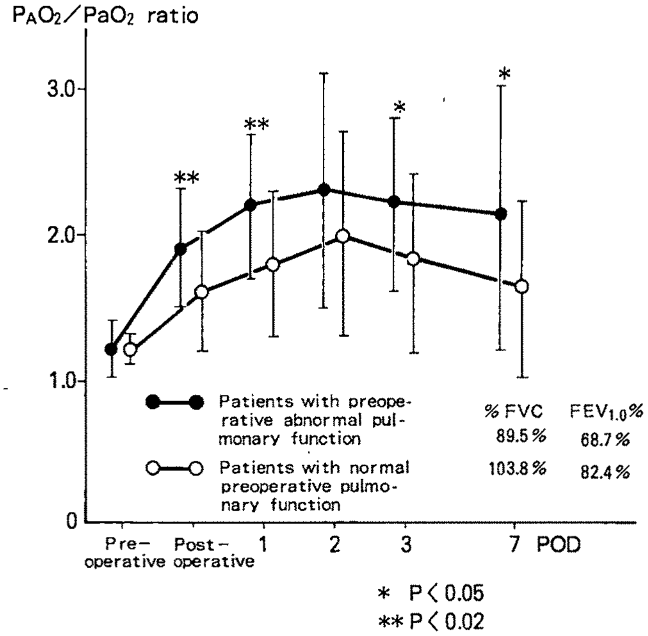

FIG. 3. Comparison of sequential measurement of oxygenation in patients with preoperative impaired pulmonary function and those with normal pulmonary function. Results are given as mean ± SD. *Statistically significant between two groups ($p < 0.05$); **$p < 0.02$.

patients over 70 years old had much more multiorgan impairment than did the control group; of 89 elderly patients, 45 (55%) showed two or more organ impairment, whereas only 21% of the control group had multiorgan impairment (Fig. 1).

With respect to the relationship between the preoperative impairment of organ function and the incidence of postoperative complications, there were no significant correlations between the two groups; however, when postoperative complications did develop in the older patients, they often progressed to multiorgan failure and death.

There were significantly lower values with respect to the nutritional assessment such as %IBW, total protein (TP), albumin (Alb), hemoglobin, and cholinesterase in the elderly patients with esophageal and/or gastric cancer, as compared to those with gallstones, whereas there were no significant differences in the measurements of organ function such as insulinogenic index ($\Delta IRI/\Delta BS$), prothrombin time, $FEV_{1.0\%}$, $\dot{V}_{25}$, GFR, and $PSP_{15'}$ between two groups.

Figure 2 illustrates the comparison between the aged and the control groups with respect to postoperative oxygenation (PAO_2/PaO_2 ratio) in patients undergoing esophagectomy and/or esophagogastrectomy for cancer. Although there were significant differences in the preoperative PAO_2/PaO_2 ratio between the elderly and the control groups, no significant difference was found after surgery. However, patients with a preoperative impairment of respiratory function showed significantly lower postoperative PAO_2/PaO_2 ratios than did the patients with no impairment (Fig. 3). These results suggest that the preoperative degree of organ impairment, rather than age, is predictive of postoperative difficulty and should be used in assessing preoperative risk.

The secretion of stress hormones in response to surgery was evaluated separately for each operative proce-

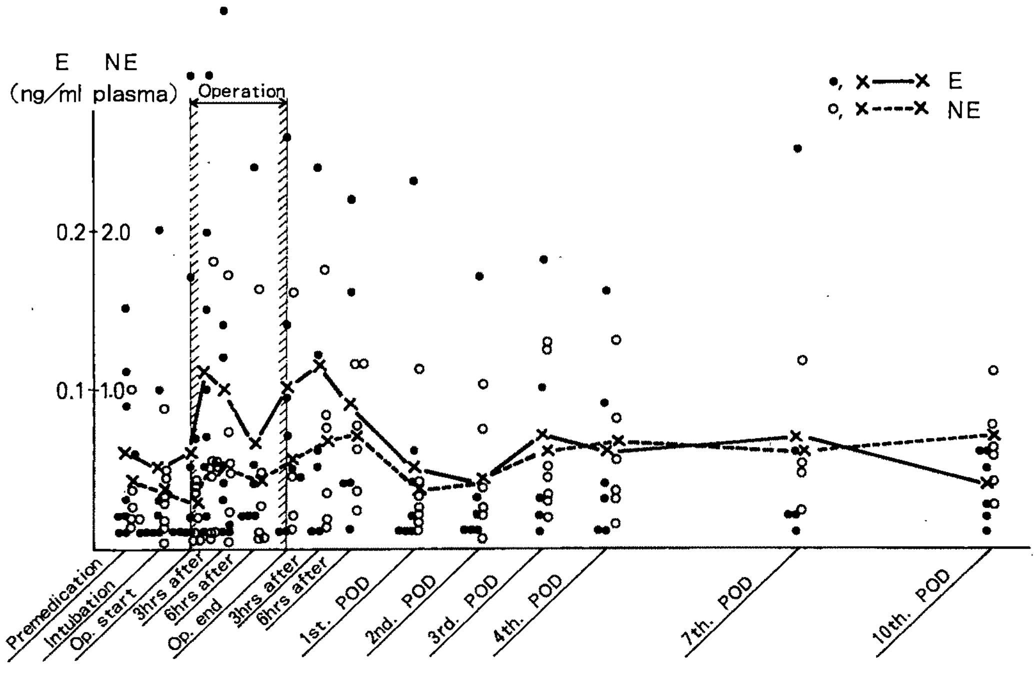

FIG. 4. Perioperative changes in the plasma catecholamine levels in patients undergoing esophagectomy for cancer.

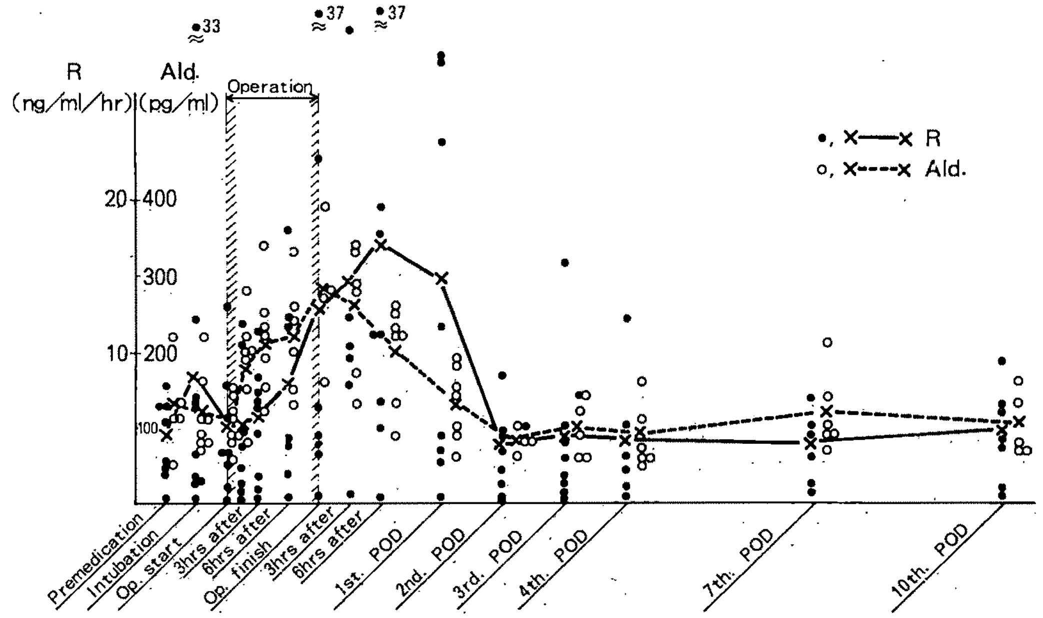

FIG. 5. Perioperative changes in the plasma renin and aldosterone levels in patients undergoing esophagectomy for cancer.

dure: esophagectomy through a combined right thoracic and abdominal approach, total gastrectomy with pancreatectomy and splenectomy, and partial gastrectomy. The plasma E level was maximally elevated at 3 hours after the initial skin incision, whereas the plasma NE reached peak levels at 6 hours after the completion of surgery (Fig. 4). There was no correlation between the plasma E levels at 3 hours after incision and the magnitude of surgical stress as indicated by the type or duration of the operative procedure, or the intraoperative blood loss. Nor was there any significant correlation between the plasma NE levels at 6 hours after the completion of surgery and the above three factors. These results indicate that the response of the plasma catecholamines to surgical stress definitely does not reflect the magnitude of stress; this finding contradicts a previous report indicating that the plasma level of catecholamines is proportional to the magnitude of surgical stress.[10]

Figure 5 shows the perioperative changes in the levels of plasma R and Ald in patients undergoing esophagectomy. The peak levels for both the plasma R and Ald were within 6 hours after the termination of surgery and returned to the preoperative levels on the second postoperative day except in one patient with chylothorax. The perioperative changes of the urinary Na/K ratio are illustrated in Figure 6, in which the lowest value was seen on the first POD, followed by a gradual return to the preoperative values.

Figure 7 illustrates the comparison between the elderly and the control groups with respect to the maxi-

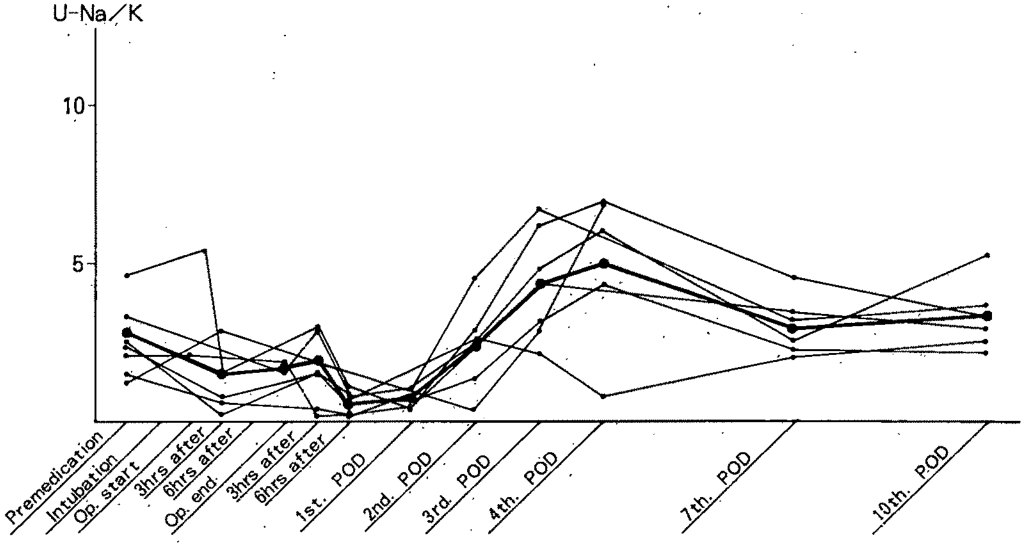

FIG. 6. Perioperative changes in the urinary Na/K ratio in patients undergoing esophagectomy for cancer.

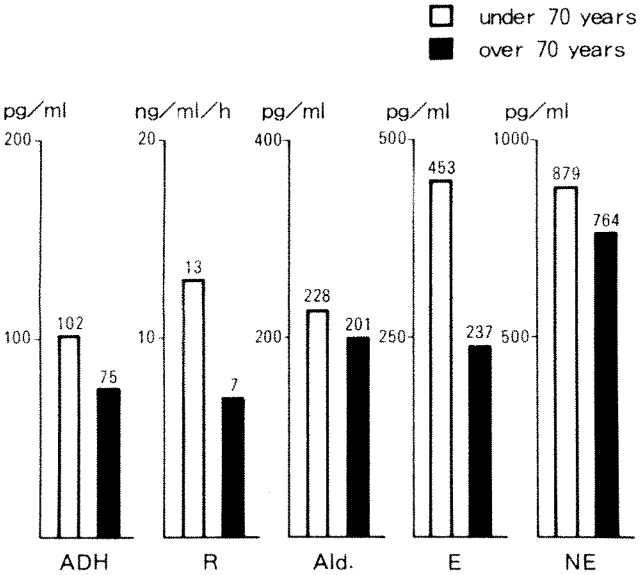

FIG. 7. Comparison between aged and control patients with respect to the peak levels of various stress hormones.

mum response (peak levels) of five stress hormones (R, Ald, ADH, E, and NE) within 24 hours after surgery in patients undergoing esophagectomy and/or gastrectomy. It was evident that the maximum responses of stress hormones in the patients over 70 were definitely decreased as compared with those of the patients under 70 years; the 50% decrease in plasma R activity and E level was particularly conspicuous.

To clarify the influence of the decreased hormonal response in the aged patients on the function of the target organ, the following studies were carried out. The plasma aldosterone levels of all patients and those of patients under 70 years showed a significant correlation with the urinary Na/K ratio, the regression lines for each group being $Y = 3.74 - 8.51X$ ($r = -0.416$, $p < 0.001$) and $Y = 4.51 - 11.4X$ ($r = -0.426$, $p < 0.001$), respectively (Fig. 8). However, there was no correlation between the plasma levels of aldosterone and the urinary Na/K ratio in the patients over 70. It seems reasonable to speculate from these results that not only does the maximum response to surgical stress become dull and the secretion of hormones get delayed, but also each target organ shows suboptimal function because of a diminished response to the appropriate stress hormone. This may be due to a diminution of hormone receptors in the target organ and/or primary end-organ impairment. These results account for the high incidence of postoperative cardiopulmonary complications in the aged.

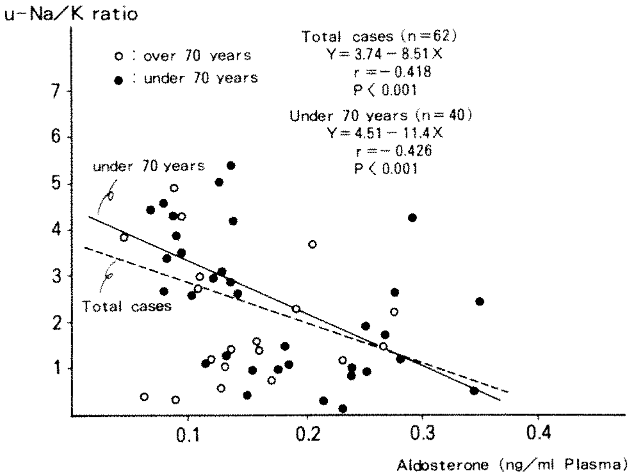

FIG. 8. Correlation between the plasma aldosterone concentration and urinary Na/K ratio during and after surgery.

Figure 9 illustrates the significant decreases in multiple nutritional parameters varying according to the stage of cancer of the esophagus, using patients with gallstones as control. An especially remarkable decrease was seen in the patients with recurrent cancer. As shown in Figure 10, an extremely close correlation, with a coefficient as high as $r = 0.56$ ($p < 0.001$), was also observed between the serum Alb levels and the total lymphocyte count in patients with esophageal cancer. Since the visceral proteins, minerals, vitamin A, and immunocompetence are all decreased with the progression of the clinical stage in patients with esophageal cancer, sufficient nutritional support is mandatory.

The incidence of anastomotic leakage in this series was 6.0% (22/364), but in esophageal cancer patients, the incidence of anastomotic leakage was surprisingly high (11/50, 22%), and in four patients this resulted in death. Several technical variations, both in surgical procedure and in the perioperative care of the patients with esophageal cancer, have been employed since 1984, such as reconstruction through the posterior mediastinum, selective endobronchial intubation during surgery, strict fluid restriction (40–45 mL/kg/d) until the third postoperative day, and immediate total parenteral and/or enteral nutrition after surgery. For the last 2 years, we have seen no life-threatening major complications such as leaks or respiratory failure, but in seven patients, some minor complications have occurred. These have included chylothorax, myocardial infarction, wound dehiscence, recurrent nerve paralysis, atelectasis, bronchopneumonia, and pleuritis. The incidence of minor complications with esophagectomy was calculated as 27%, and none of these esophagectomized patients died within 1 month of the operation. Furthermore, no postoperative hospital deaths have occurred for the past 2 years.

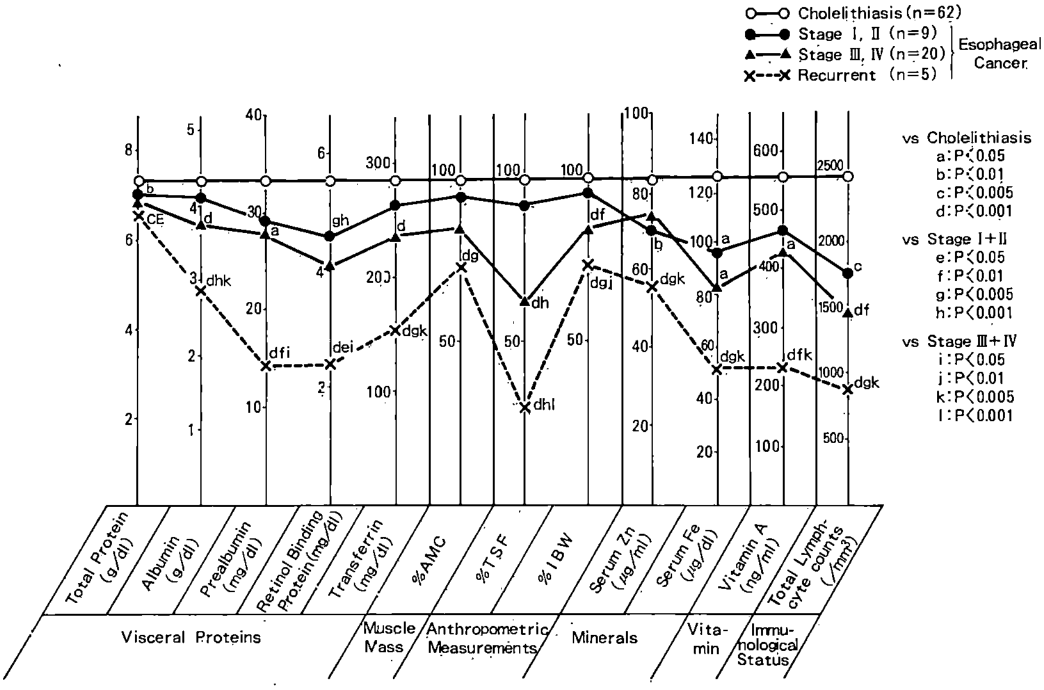

FIG. 9. Nutritional and immunologic parameters in patients with esophageal cancer of different stage. Patients with cholelithiasis were used as a control group. Results are given as the mean values.

Discussion

In surgical patients, a catabolic response occurs as a result of the stress hormones released after surgery in proportion to the magnitude of stress. However, the half-lives of several stress hormones in plasma are so short (minutes) that scrupulous caution is needed in measuring them. For example, the half-life of the plasma catecholamines is extremely short, less than 2 minutes after release into the bloodstream.[11]

It has been previously reported that there is a significant correlation between the plasma concentrations of NE at maximum levels and the magnitude of stress such as the type of operative procedure, blood loss during surgery, and the duration of surgery.[10] We found no correlation among these factors, leading us to presume that there were differences in the times of measurement. The plasma catecholamine levels in surgical patients fluctuate in response to the kind of anesthesia used, the volume of blood lost during surgery, and the posture of the patients during surgery.[12,13] In general, epidural anesthesia may inhibit plasma catecholamine secretion and, therefore, reduce the postoperative catabolic response, whereas the levels of plasma catecholamine are increased by the induction of neuroleptanalgesia.[14] The plasma NE levels during surgery are not an accurate index for the magnitude of the surgical stress. Generally speaking, it is thought that delayed and inadequate responsiveness, prolonged recovery from the catabolic phase, and poor adaptation are the characteristic features of elderly patients with respect to their metabolic response to surgical stress. In the present study, however, we found that although the response pattern to surgical stress in elderly patients is not essentially different from that of patients under 70 years, the peak levels of stress hormones are retarded and diminished in the elderly. Furthermore, it becomes evident that the poor correlation in the aged group between the plasma aldosterone levels and the urinary Na/K ratio may reflect a retarded response to the hormone or a primary loss of function of the target organ.

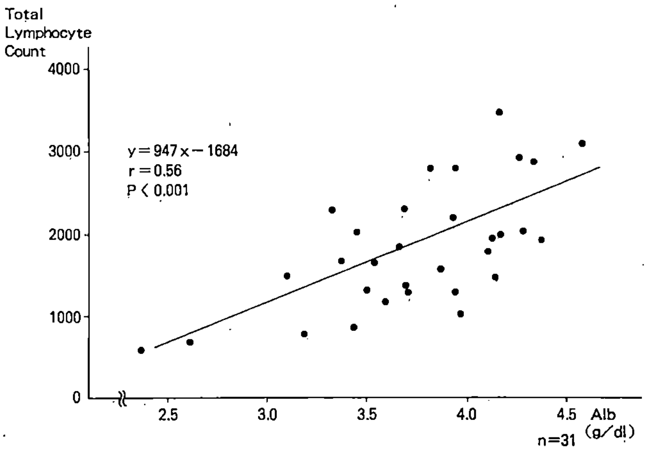

FIG. 10. Correlation between total lymphocyte count in peripheral blood and serum albumin levels in patients undergoing esophagectomy for cancer.

If the excess response of the sympathetic nervous system and adrenal axis to surgical stress could be suppressed, more stable cardiopulmonary function during surgery and a reduction in the excessive and undesirable catabolic reactions after surgery might be achieved. Berk et al.[15] have suggested that the use of β-adrenergic blockers could reduce these catabolic reactions. Further studies on the proper anesthesia and surgery to minimize the stress response are required.

The many risk factors that contribute to postoperative complications following esophagectomy with thoracotomy for cancer have been listed in the literature.[16] Among these factors, chronic bronchitis and preoperative irradiation have been particularly significant risks that increase the chance of the postoperative development of pulmonary complications. The present study discloses that there is a significant correlation between the postoperative development of complications and the preoperative impairment of the respective organs in aged patients. With respect to perioperative replacement therapy, it is clearly necessary to maintain an adequate circulating blood volume and to prevent acute renal insufficiency during and after surgery. Therefore, sufficient infusions should be given to prevent early postoperative hypovolemia, as proposed by Ando et al.[17] However, until the third postoperative day, it is recommended to restrict fluids as evidenced by the present studies on hormonal response.

Since the pulmonary complications following the use of mechanical ventilation postoperatively increase significantly with its duration, one must take this into consideration. Recently, it has been advocated that selective endobronchial intubation was associated with fewer postoperative pulmonary complications than endotracheal intubation. Our results in this series confirmed these reports.

The improvement of the nutritional status of patients with cancer through nutritional support can reduce the operative mortality and morbidity rates. Nutritional assessment is important for this purpose. It is essential in the formulation of nutritional supplements and in judging its effects for rational preoperative and postoperative nutritional support.

In general, the average nutritionally depleted or complicated cancer patients requires between 40 and 50 kcal/kg/d with simultaneous administration of 150 to 200 nonprotein calories/g nitrogen.

If the poor nutritional status of cancer patients on admission can be improved by adequate preoperative nutritional support, the incidence of postoperative complications, including anastomotic leakage, can be considerably reduced.

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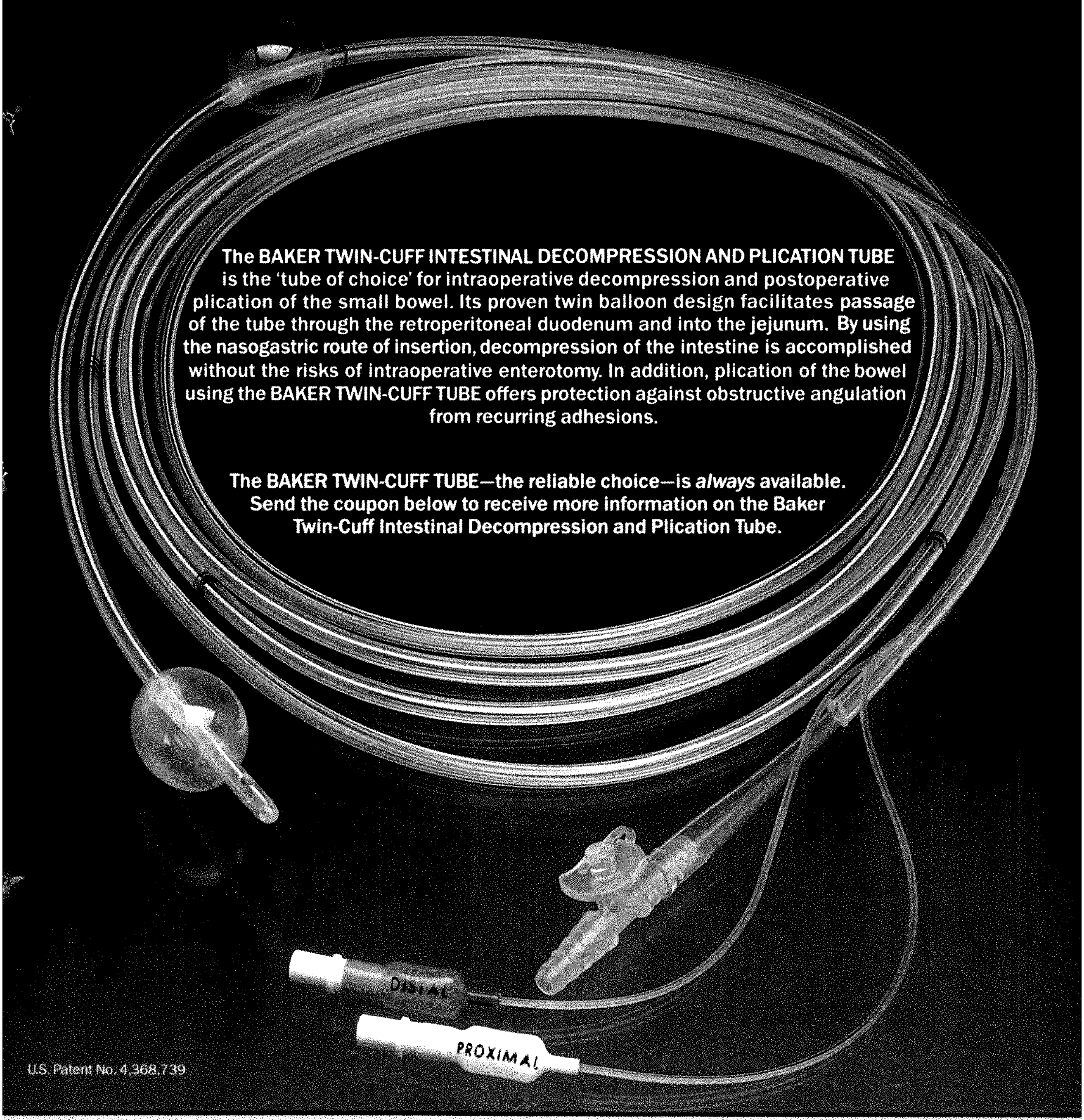

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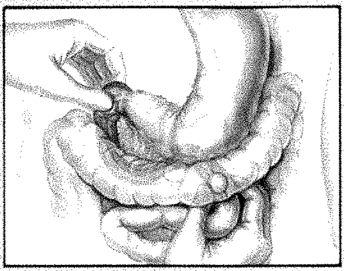

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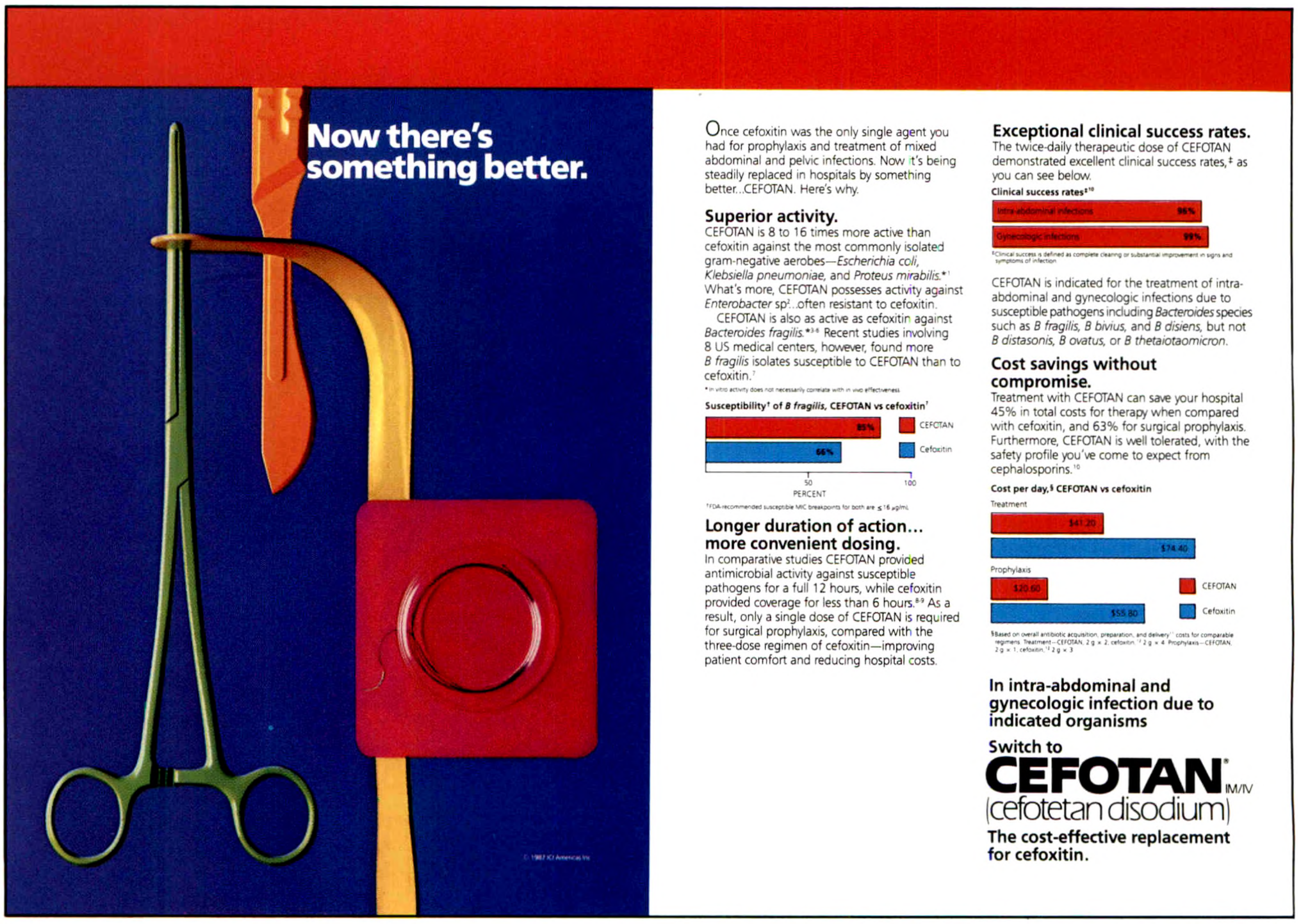

Now there's something better.

Once cefoxitin was the only single agent you had for prophylaxis and treatment of mixed abdominal and pelvic infections. Now it's being steadily replaced in hospitals by something better...CEFOTAN. Here's why.

Superior activity.

CEFOTAN is 8 to 16 times more active than cefoxitin against the most commonly isolated gram-negative aerobes—*Escherichia coli, Klebsiella pneumoniae*, and *Proteus mirabilis*.*[1] What's more, CEFOTAN possesses activity against *Enterobacter* sp[2]...often resistant to cefoxitin.

CEFOTAN is also as active as cefoxitin against *Bacteroides fragilis*.*[3-6] Recent studies involving 8 US medical centers, however, found more *B fragilis* isolates susceptible to CEFOTAN than to cefoxitin.[7]

*In vitro activity does not necessarily correlate with in vivo effectiveness.

Susceptibility† of *B fragilis*, CEFOTAN vs cefoxitin[7]

†FDA-recommended susceptible MIC breakpoints for both are ≤16 μg/mL

Longer duration of action... more convenient dosing.

In comparative studies CEFOTAN provided antimicrobial activity against susceptible pathogens for a full 12 hours, while cefoxitin provided coverage for less than 6 hours.[8-9] As a result, only a single dose of CEFOTAN is required for surgical prophylaxis, compared with the three-dose regimen of cefoxitin—improving patient comfort and reducing hospital costs.

Exceptional clinical success rates.

The twice-daily therapeutic dose of CEFOTAN demonstrated excellent clinical success rates,‡ as you can see below.

Clinical success rates‡[10]

‡Clinical success is defined as complete clearing or substantial improvement in signs and symptoms of infection

CEFOTAN is indicated for the treatment of intra-abdominal and gynecologic infections due to susceptible pathogens including *Bacteroides* species such as *B fragilis, B bivius*, and *B disiens*, but not *B distasonis, B ovatus*, or *B thetaiotaomicron*.

Cost savings without compromise.

Treatment with CEFOTAN can save your hospital 45% in total costs for therapy when compared with cefoxitin, and 63% for surgical prophylaxis. Furthermore, CEFOTAN is well tolerated, with the safety profile you've come to expect from cephalosporins.[10]

Cost per day,§ CEFOTAN vs cefoxitin

§Based on overall antibiotic acquisition, preparation, and delivery[11] costs for comparable regimens. Treatment—CEFOTAN, 2 g × 2; cefoxitin,[12] 2 g × 4. Prophylaxis—CEFOTAN, 2 g × 1; cefoxitin,[12] 2 g × 3

In intra-abdominal and gynecologic infection due to indicated organisms

Switch to

CEFOTAN® IM/IV

(cefotetan disodium)

The cost-effective replacement for cefoxitin.

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1. Journal Advertisement, *N Engl J Med*, 1987.

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They said.[2-9]

for treatment in obstetrics and gynecology

"Twice-daily administration of cefotetan is a highly effective single agent for the treatment of mixed aerobic-anaerobic infections in obstetric and gynecologic patients."[2]

2. Sweet RL, Gall SA, Gibbs RS, et al: Multicenter clinical trial comparing cefotetan versus moxalactam or cefoxitin as therapy for obstetric and gynecologic infections. *Am J Surg*, submitted for publication.

"Cefotetan plus doxycycline was demonstrated to be an effective and safe regimen for the treatment of acute PID as measured by early clinical response."[3]

3. Sweet RL, Schacter J, Landers DV, et al: Treatment of hospitalized patients with acute pelvic inflammatory disease: Comparison of cefotetan plus doxycycline and cefoxitin plus doxycycline. *Am J Obstet Gynecol*, submitted for publication.

for treatment in intra-abdominal infection

"98% (93/95) of cefotetan patients and 95% (41/43) of cefoxitin patients had complete resolution or improvement of their signs and symptoms of intraabdominal infection."[4]

4. Wilson SE for the Multicenter Study Group: Cephalosporin therapy in intraabdominal infections: A multicenter randomized comparative study of cefotetan, moxalactam and cefoxitin. *Am J Surg*, submitted for publication.

for prophylaxis in obstetric and gynecologic surgery

"In this evaluation, cefotetan administered in a single dose of 1 gm was more effective as a prophylactic agent than multiple, 2-gm doses of cefoxitin in reducing infectious morbidity in...cesarean section patients."[5]

5. McGregor JA, Gordon SF, Krotec J, et al: Results of a randomized, multicenter, comparative trial of a single dose of cefotetan versus multiple doses of cefoxitin as prophylaxis in cesarean section. *Am J Obstet Gynecol*, submitted for publication.

"Uterine tissue concentration was...well above the minimum inhibitory concentrations required for most gram-positive anaerobes as well as Bacteroides fragilis."[6]

6. Berkeley AS, Freedman KS, Ledger WJ, et al: Comparison of cefotetan and cefoxitin for abdominal and vaginal hysterectomy. *Am J Obstet Gynecol*, submitted for publication.

for prophylaxis in general surgery

"Cefotetan administered as a single 2-gm preoperative dose was as safe and effective as multiple doses of cefoxitin."[7]

7. Jagelman DG, Fabian TC, Nichols RL, et al: Single-dose cefotetan vs. multiple-dose cefoxitin as prophylaxis in colorectal surgery. *Am J Surg*, submitted for publication.

as a cost-effective replacement for cefoxitin

*"Cefotetan therapy cost less than cefoxitin therapy for all types of infections."**[8]

8. Sochalski A, Sullman S, Andriole VT: Cost effectiveness study of cefotetan versus cefoxitin and cefotetan versus combination antibiotic regimens. *Am J Surg*, submitted for publication.

"Cefotetan can provide significant cost savings with neither a compromise in therapeutic effectiveness nor an increased risk of toxicity."[9]

9. Hemsell DL, Wendel GD, Gall SA, et al: Multicenter comparison of cefotetan and cefoxitin in the treatment of obstetric and gynecologic infections. *Am J Obstet Gynecol*, submitted for publication.

*CEFOTAN is indicated for the treatment of intra-abdominal and gynecologic infections due to susceptible pathogens including *Bacteroides* species such as *B fragilis*, *B bivius*, and *B disiens*, but not *B distasonis*, *B ovatus*, or *B thetaiotaomicron*.

We all agree.

CEFOTAN® IM/IV
(cefotetan disodium)

Does so much for so much less than cefoxitin

Please see next page for brief summary of prescribing information.

In intra-abdominal and gynecologic infection due to indicated organisms

CEFOTAN® IM/IV

(cefotetan disodium)

Does so much for so much less than cefoxitin

For Intravenous or Intramuscular Use
BRIEF SUMMARY

INDICATIONS AND USAGE
TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:
Urinary tract infections caused by *E coli, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris, Providencia rettgeri,* and *Morganella morganii*).
Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli.*
Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis,** *Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli.*
Gynecologic infections caused by *Staphylococcus aureus*† (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis,** *Streptococcus* species (excluding enterococci), *E coli, Proteus mirabilis, Neisseria gonorrhoeae, Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*), *Fusobacterium* species,† and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species†).
Intra-abdominal infections caused by *E coli, Klebsiella* species (including *K pneumoniae*†), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*).
Bone and joint infections caused by *Staphylococcus aureus.*†
***NOTE:** Some strains of *Staphylococcus epidermidis* are resistant to cefotetan.
† Efficacy for this organism in this organ system was studied in fewer than ten infections.
PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS
CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS
Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile.* Other causes should also be considered.

PRECAUTIONS
GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state. Prothrombin times should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.
INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.
DRUG INTERACTIONS: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.
DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels of Jaffe reaction and produce false increases in the levels of creatinine reported.
CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approx 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approx 2-4 times the usual human dose), only 1 of 10 treated animals was affected, and the degree of degeneration was mild. Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.
PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
In clinical studies the following adverse effects were considered related to CEFOTAN therapy.
Gastrointestinal symptoms occurred in 1.5 percent of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).
Hematologic laboratory abnormalities occurred in 1.4 percent of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).
Hepatic enzyme elevations occurred in 1.2 percent of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).
Hypersensitivity reactions were reported in 1.2 percent of patients and included rash (1 in 150) and itching (1 in 700).
Local effects were reported in less than one percent of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

DOSAGE AND ADMINISTRATION
TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.
IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dose*	Every 12 hours
10-30	Usual Recommended Dose*	Every 24 hours
<10	Usual Recommended Dose*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED
CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.
1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21)

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Rev E 3/86

Treatment of the Dumping Syndrome with the Somatostatin Analogue SMS 201-995

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In six patients suffering from severe early dumping and six patients with late dumping after peptic ulcer surgery, the effect of the somatostatin analogue SMS 201-995 was compared with placebo. In early dumpers subcutaneous administration of 50 µg SMS 201-995 prior to meal ingestion induced a strong improvement of dumping symptoms as reflected by a decrease of the Sigstad dumping score from 12 $\pm$ 2 during placebo to 5 $\pm$ 2 ($p < 0.05$). Furthermore, the postprandial increase of pulse rate was abolished; maximum pulse rate decreased from 85 $\pm$ 7 beats/min to 67 $\pm$ 7 beats/min ($p < 0.05$). SMS 201-995 did not significantly affect postprandial changes in packed cell volume. In late dumpers 50 µg SMS 201-995 reduced peak plasma insulin after oral glucose from 173 $\pm$ 16 mU/L during placebo to 35 $\pm$ 9 mU/L during SMS 201-995 ($p < 0.05$) and increased individual plasma glucose nadirs from 1.9 $\pm$ 0.3 mmol/L to 7.5 $\pm$ 3.3 mmol/L ($p < 0.01$). Both in early and late dumpers SMS 201-995 improved postprandial expiratory breath hydrogen excretion indicating slowing of gastrointestinal hurry. SMS 201-995 is a powerful therapeutic agent for the management of patients suffering from the dumping syndrome after gastric surgery.

THE DUMPING SYNDROME can be a serious and disabling complication after gastric surgery.[1–3] The syndrome is precipitated especially by heavy or carbohydrate-rich meals (1–3). Symptoms of early dumping occur during or immediately after meal ingestion and consist of both gastrointestinal and cardiovascular components including nausea, epigastric distress, meteorismus, borborygmia, palpitation, weakness, exhaustion, dyspnea, dizziness, and syncope.[2] The symptoms of late dumping including a feeling of warmth, sweating, shakiness, dizziness and difficulty in concentration occur 1 to 3 hours later and are attributed to reactive postprandial hypoglycemia.[3] Rapid gastric emptying of hyperosmolar food resulting in a shift of water and elektrolytes to the small intestinal lumen with subsequent hemoconcentration and abnormal gut endocrine responses are generally thought to play a crucial role in the pathogenesis of the syndrome.[1–7] So far, methods of treatment including dietary fibers and α-glucosidase inhibitors have met with only limited success.[8–11] Recently, it has been suggested that somatostatin and possibly its analogues might be of value in the management of circulatory and metabolic disturbances associated with the syndrome.[12] The present study was therefore undertaken to determine the effect of SMS 201-995, a long-acting analogue of somatostatin, on clinical symptoms, pulse rate, packed cell volume, plasma insulin, plasma glucose, and breath hydrogen excretion in patients suffering from postprandial dumping.

Patients and Methods

Six patients (three men, three women; 33–48 years) with early dumping selected on the basis of the clinical diagnostic index divised by Sigstad[13] participated in the study. All patients had undergone a partial gastric resection for peptic ulcer disease at least 1 year before. In addition, six patients (three men, three women; 26–48 years; one highly selective vagotomy, five partial gastrectomy) with late dumping were studied. These patients were selected on the basis of having a history suggestive of postprandial hypoglycemia, a plasma glucose of less than 3.0 mmol/L at least 60 minutes after ingestion of 50 g glucose/m^2 body surface, and hypoglycemic

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Submitted for publication: August 13, 1987.

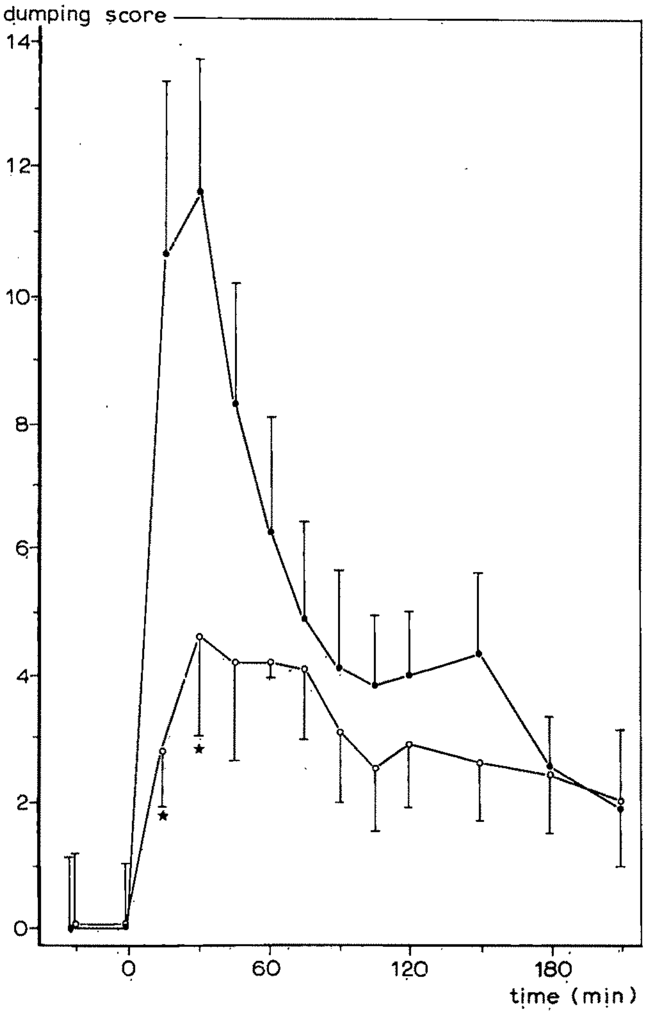

FIG. 1. Numerical dumping score after oral glucose with SMS 201-995 (O) and without SMS 201-995 (●) in six patients with early dumping. *Significant differences from placebo.

symptoms at least 60 minutes after the oral glucose load. Each patient was studied on two occasions after an overnight fast. In random order and in a double-blind fashion either 50 μg SMS 201-995 or placebo was administered subcutaneously 15 minutes before ingestion of 50 g glucose/m^2 body surface. Before ingestion of the 50% glucose solution in water and at regular intervals thereafter, patients were questioned about their symptoms and allocated a dumping score according to Sigstad.[13] Pulse rate was counted and blood samples were drawn at −25, −20, −15, 0, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180, 195, and 210 minutes. Before ingestion of the meal and at 30-minute intervals during the study, end-expiratory gas samples were obtained for measurement of breath hydrogen.[14] In the patients with early dumping the blood samples were used to measure packed cell volume. In patients with late dumping, these samples served to measure plasma glucose and plasma insulin levels.[15] Packed cell volume and plasma glucose were measured by standard techniques.

Results were expressed as the mean ± 1 SEM. Statistical analysis was performed by Student's t-test for paired results. Wilcoxon's test for paired data was used to analyse dumping score. All patients gave informed consent before entering the study. The study was approved by the local ethical committee.

Results

Early Dumpers

During placebo injection dumping score increased to a peak value of 11.7 ± 2.1 at 30 minutes after meal ingestion indicating severe dumping (Fig. 1). During SMS 201-995 all patients experienced a dramatic improvement of postprandial symptoms. At 15 and at 30 minutes, dumping score during SMS 201-995 was sig-

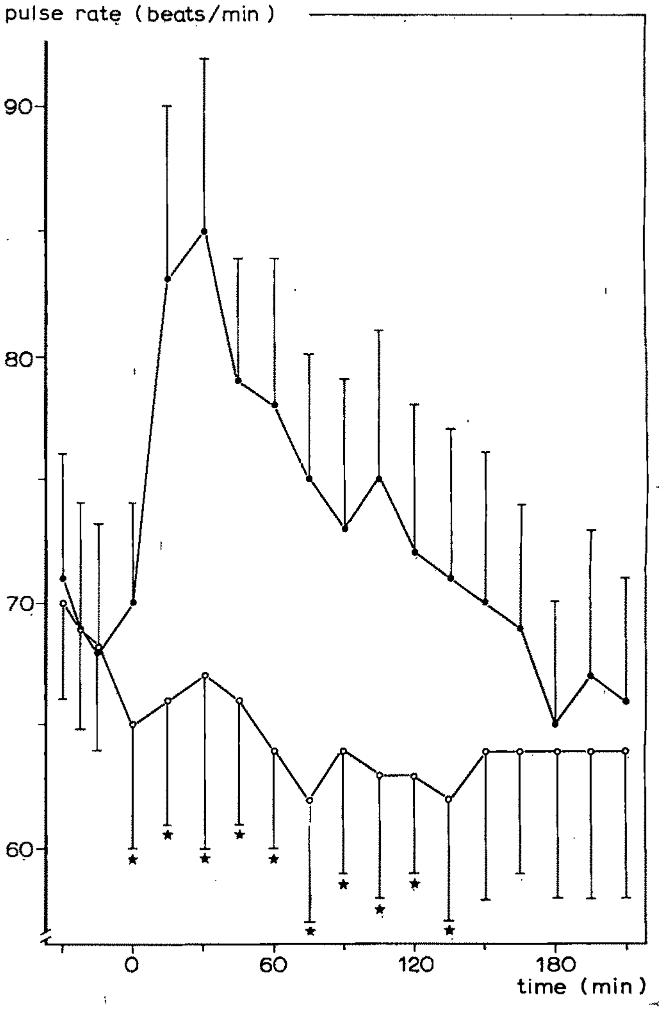

FIG. 2. Pulse rate after oral glucose with SMS 201-995 (O) and without SMS 201-995 (●) in six patients with early dumping. *Significant differences from placebo.

nificantly lower than that during placebo ($p < 0.05$, Fig. 1). Maximum dumping score during SMS 201-995 was 4.6 ± 1.6 at 30 minutes ($p < 0.05$ *vs.* placebo). Pulse rate increased from a basal value of 70 ± 4 beats/min to a maximum value of 85 ± 7 beats/min at 30 minutes after meal ingestion during placebo ($p < 0.05$, Fig. 2). On the other hand, SMS 201-995 abolished this postprandial rise in pulse rate (Fig. 2). Pulse rate during SMS 201-995 was significantly lower than that during placebo from 0 to 135 minutes ($p < 0.05$ to $p < 0.005$, Fig. 2).

Packed cell volume rose from 0.38 ± 0.02 L/L to 0.41 ± 0.02 L/L at 30 minutes during placebo ($p = 0.0005$, Fig. 3), and from 0.39 ± 0.02 L/L to 0.41 ± 0.02 L/L during SMS 201-995 ($p < 0.05$, Fig. 3). No significant differences were observed between packed cell volume during placebo and packed cell volume during SMS 201-995.

Four patients had a breath hydrogen excretion of more than 15 ppm during placebo at 30–60 minutes indicating spillover of glucose to the colon, but only one patient during SMS 201-995 at 150 minutes.

Late Dumpers

In patients suffering from reactive hypoglycemia, the initial rapid rise in plasma glucose was followed by a sharp decline to levels below 3.0 mmol/L from 105 to 135 minutes after the oral glucose load (Fig. 4). The reactive hypoglycemia observed during the placebo study was completely abolished by subcutaneous administration of SMS 201-995. From 60 to 210 minutes plasma glucose during SMS 201-995 was significantly higher than that during placebo ($p < 0.05$ to $p < 0.0005$, Fig. 4). Individual plasma glucose nadirs during placebo were 1.9 ± 0.3 mmol/L. During SMS 201-995 lowest individual plasma glucose levels were 7.5 ± 3.3 mmol/L ($p < 0.001$). SMS 201-995 attenuated plasma insulin response to glucose ingestion. Plasma insulin during SMS 201-995 was significantly lower than that during placebo at 30 and at 60 minutes ($p < 0.05$ to $p < 0.01$, Fig. 5). Peak plasma insulin level decreased from 173 ± 16 mU/L during placebo to 35 ± 9 mU/L during SMS 201-995 ($p < 0.05$). No patient experienced hypoglycemic symptoms during SMS 201-995. Three patients had a breath hydrogen excretion of more than 15 ppm during placebo at 15–60 minutes. On the other hand, during SMS 201-995 no patient presented with abnormal breath hydrogen excretion.

Discussion

SMS 201-995 is a recently developed, long-acting analogue of somatostatin.[16] The circulating half-life of SMS 201-995 of about 100 minutes after subcutaneous injection is substantially longer than that of native somato-

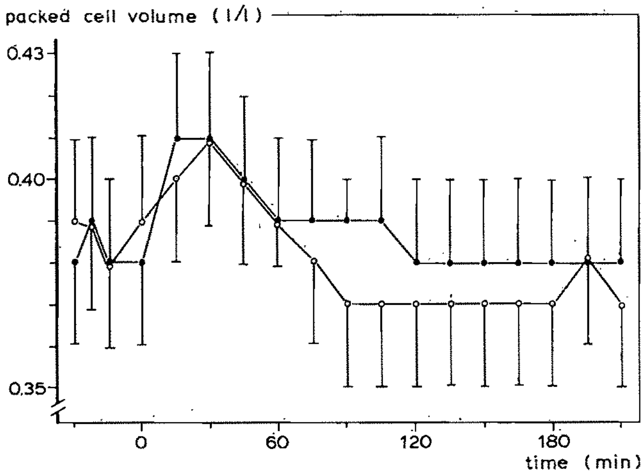

FIG. 3. Packed cell volume after oral glucose with SMS 201-995 (O) and without SMS 201-995 (●) in six patients with early dumping.

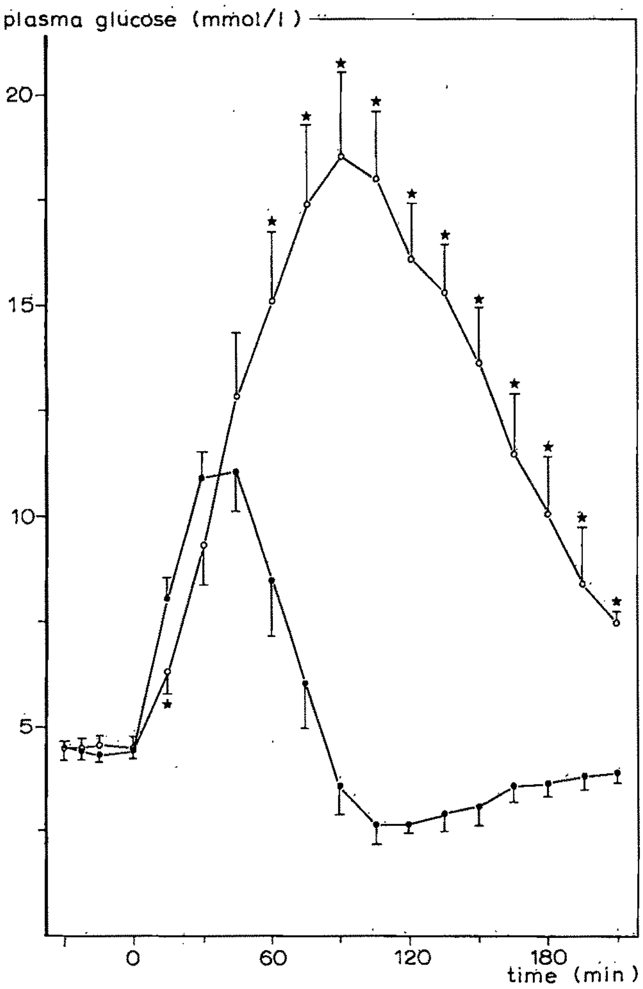

FIG. 4. Plasma glucose after oral glucose with SMS 201-995 (O) and without SMS 201-995 (●) in six patients with late dumping. *Significant differences from placebo.

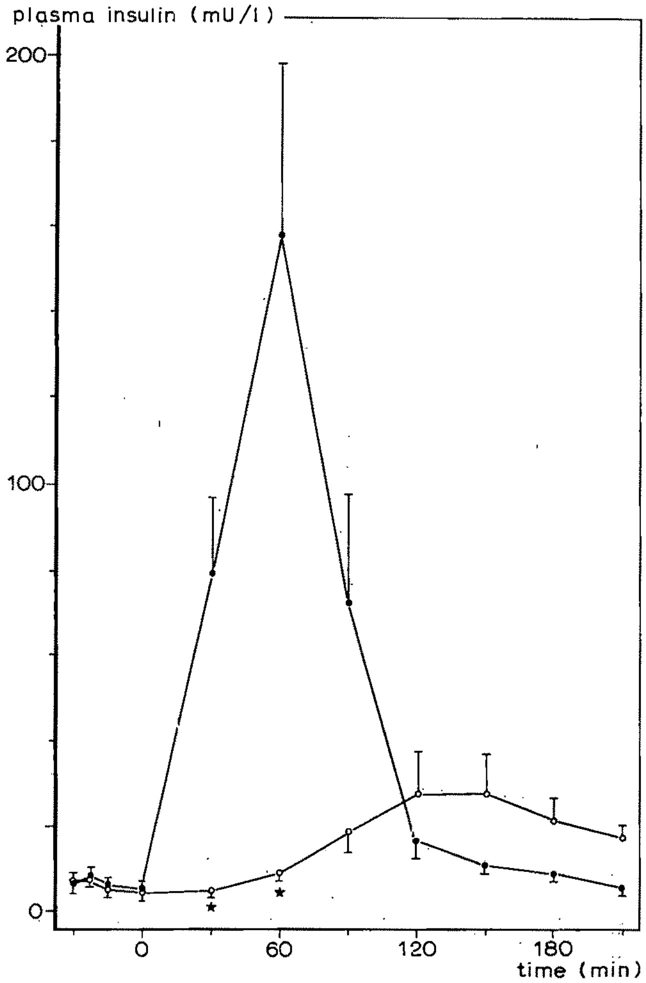

FIG. 5. Plasma insulin after oral glucose with SMS 201-995 (O) and without SMS 201-995 (●) in six patients with late dumping. *Significant differences from placebo.

statin, which is only 2 to 3 minutes.[16] SMS 201-995 inhibits release of growth hormone, and it has been used successfully in the treatment of patients with acromegaly.[17] Similar to native somatostatin, SMS 201-995 inhibits release of several gastrointestinal peptides including insulin, glucagon, gastrin, gastric inhibitory polypeptide, pancreatic polypeptide, vasoactive intestinal polypeptide, and neurotensin.[18] SMS 201-995 was found to have a beneficial effect in the management of patients with insulinoma, glucagonoma, VIPoma, and carcinoid syndrome.[19,20]

The present study shows a dramatic improvement of postprandial dumping symptoms after subcutaneous injection of SMS 201-995 prior to meal ingestion in patients with previous gastric surgery. All patients with early dumping participating in the study suffered from severe postprandial complaints that had resisted other therapeutic efforts including addition of pectin or acarbose, an α-glucosidase inhibitor, to the meal. In these patients dumping score decreased from 12 to 5. McLoughlin et al.[9] treated patients with less severe dumping symptoms with acarbose. In these patients an improvement of the dumping score from only 6 to 4 was reported. Furthermore, during SMS 201-995, postprandial rise of pulse rate, a symptom associated with the dumping syndrome, was completely abolished. This action agrees with that of native somatostatin in dumping patients.[12]

The mechanism by which SMS 201-995 exerts its beneficial effect on postprandial dumping is not known. Somatostatin slows gastrointestinal transit.[21] Since rapid gastric emptying of food is generally considered to be of major importance in precipitating the dumping syndrome, the effect of SMS 201-995 might be mediated by slowing of gastrointestinal transit. Indeed, it was shown in the present study that abnormal breath hydrogen excretion indicating spillover of glucose to the colon, resulting from the rapid transit, became normal in three out of four patients with early dumping. An increase in postprandial splanchnic blood flow, together with a paradoxical increase of subcutaneous blood flow (plus a decrease in circulatory blood volume) has been suggested to be involved in the development of cardiovascular symptoms.[1,2,6] Because postprandial increase of packed cell volume was not significantly affected by SMS 201-995, it is unlikely that SMS 201-995 exerted its beneficial effect by preventing plasma volume depletion. On the other hand, the beneficial effect of SMS 201-995 on circulatory disturbances might be related to a direct pressor effect on splanchnic hemodynamics. Indeed, it was recently reported that SMS 201-995 inhibited splanchnic blood flow similar to native somatostatin.[22,23] Furthermore, a pressor effect of SMS 201-995 was demonstrated in patients suffering from postprandial hypotension.[24] Another possibility is that SMS 201-995 similar to native somatostatin inhibited excessive release of vasoactive substances from the gut that have been incrementated in the pathogenesis of circulatory disturbances.[1,2,4,5,7,12] It is interesting to note that SMS 201-995 also improved circulatory symptoms in patients with the carcinoid syndrome.[20]

In patients suffering from late dumping, SMS 201-995 was highly effective for the prevention of reactive hypoglycemia. Even after administration of a powerful challenge of carbohydrate metabolism by a concentrated glucose meal, during SMS 201-995 the lowest plasma glucose level was well above hypoglycemic values. No complaints of hypoglycemia were reported during SMS 201-995. The beneficial effect of SMS 201-995 is probably related to inhibition of excessive insulin release in the early postprandial phase as demonstrated in the present study. Furthermore, inhibition of intestinal hurry as reflected by breath hydrogen excretion allowing glucose to be present in the small intestine for absorption in the late postprandial phase, probably contributes to the beneficial effect of SMS 201-995. α-Glucosidase inhibitors have been recommended in patients suffering from postprandial reactive hypoglycemia.[9–11] However, these substances induced serious side effects due to malabsorption of carbohydrates.[10,11] In contrast, SMS 201-995 subsided malabsorption of carbohydrates in all patients with late dumping.

Long-term studies have demonstrated good tolerance of SMS 201-995 in the treatment of patients with acromegaly, carcinoid syndrome, and other endocrine tumors of the gut.[17,19,20,24,25] In these patients no serious side effects were reported. Similarly, in the present study SMS 201-995 was well tolerated by all patients without any side effects.

We conclude that SMS 201-995 is highly effective for the prevention of symptoms and signs related to the dumping syndrome. It reduces tachycardia and peak plasma insulin level, and it prevents reactive hypoglycemia with spillover of glucose to the colon. Since SMS 201-995 is well tolerated, it holds promise as a powerful therapeutic agent in patients with disabling postprandial dumping after previous gastric surgery.

Acknowledgments

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Intraoperative Ultrasonographic Localization of Islet Cell Tumors

A Prospective Comparison to Palpation

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The purpose of the present study was to evaluate prospectively the value of intraoperative ultrasound scanning (IOUS) in localizing islet cell tumors by comparing results of IOUS to those of palpation during 44 consecutive laparotomies for gastrinoma (36) or insulinoma (8). All patients had preoperative radiographic imaging studies and selective venous sampling for hormones, which guided the subsequent laparotomy. Any suspicious finding by palpation and/or IOUS was resected. Pathologic evidence of islet cell neoplasm served as the reference standard. Five patients were excluded from analysis because neither palpation nor IOUS had suspicious findings and no islet cell tumor was found. Seven pancreatic insulinomas were found in seven patients. IOUS was as sensitive as palpation at localizing insulinomas. Twenty-three pancreatic gastrinomas were found in 19 patients. IOUS was equal to palpation in the ability to localize gastrinomas. Gastrinomas that were successfully imaged by IOUS were significantly larger than gastrinomas that were not imaged. Twelve extrapancreatic gastrinomas were found in nine patients, and palpation was more sensitive than IOUS at localizing these small duodenal wall tumors. Five patients (11%) had their surgical management changed by IOUS. Two patients had pancreatic tumors (one gastrinoma and insulinoma) enucleated that would not have been found without IOUS, and three patients had resections of pathologically proven malignant islet cell tumors based on sonographic findings. All five patients were *cured* with short follow-up. The present results demonstrate that palpation and IOUS are complementary because IOUS can image tumors that are not palpable and IOUS can provide additional information concerning malignant potential not detected by palpation.

TUMOR LOCALIZATION is a major problem associated with endocrine tumors. Small islet cell tumors produce hormones that lead to early diagnosis and potential surgical intervention. Despite careful search at laparotomy, insulinomas and gastrinomas are occult and elusive. Blind subtotal pancreatectomy with the increased morbidity and mortality rate is necessary when an insulinoma cannot be found.[1] Gastrinomas are more elusive than insulinomas and have been localized in only 60–73% of laparotomies for Zollinger-Ellison syndrome (ZES).[2-4] Preoperative localization procedures, including selective arteriography,[5] CT scanning with contrast,[6] and transhepatic portal venous sampling for hormones,[7] have not solved the problem of islet cell tumor localization.

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In 1982 the use of high-resolution B-mode IOUS scanning to image an insulinoma[8] and a gastrinoma[9] was first reported. In 1985 operative sonography successfully localized a small insulinoma, which had not been palpable in the pancreatic head.[10] We have had a large experience with insulinoma[11] and gastrinoma.[12] To evaluate the potential usefulness of IOUS to find small, surgically curable insulinomas and gastrinomas, we instituted a prospective comparison of IOUS to palpation in 1983. We have briefly described the first 10 gastrinoma patients.[13] We now analyze our results in 44 consecutive patients: 36 patients with gastrinoma and 8 patients with insulinoma.

Methods

In October 1983, a prospective study of the ability of IOUS to localize islet cell neoplasms in patients with either insulinoma or gastrinoma was instituted. All patients were treated at the National Institutes of Health using approved protocols.

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The diagnosis of insulinoma was established by an inappropriate elevation of serum insulin level and hypoglycemia following a fast.[11] The diagnosis of ZES was established using the following criteria: (1) elevated fasting serum gastrin concentration (> 100 pg/mL); (2) basal acid output greater than 15 mEq/h (no previous gastric surgery); and (3) abnormal provocative secretin or calcium test defined as an increase in serum gastrin concentration of greater than 200 pg/mL following the I.V. administration of 2 U/kg of GIH secretin or greater than 395 pg/mL after calcium (5 mg/kg/h × 3 hours).[4]

All patients had preoperative localization studies, namely, ultrasound, computed tomography, selective ateriography, and percutaneous transhepatic portal venous sampling (PVS).[4–8] A hormone (either gastrin or insulin) gradient of 50% (selective portal venous hormone concentration/simultaneous peripheral venous concentration) was considered to be regionally localizing to the head, body, or tail of the pancreas.[7] As outlined previously,[4] all patients with metastatic tumor to the liver or with multiple endocrine neoplasia type I without positive results from imaging studies were excluded from this study. Final surgical pathology served as the reference standard for all intraoperative localization maneuvers.

All operations were performed as previously described.[4] The liver, pelvis, small intestine, pancreas, stomach, duodenum, mesenteric, and retroperitoneal regions were carefully explored. The pancreas was examined visually and by palpation. The pancreatic head was inspected after an extended Kocher maneuver. The pancreatic body and tail were inspected by opening the lesser sac along the avascular plane of the transverse colon. The inferior border of the pancreas was dissected free, so the body and tail could be palpated between two fingers. The entire duodenum was carefully palpated. The same extensive search was made regardless of the preoperative localization information or the operative findings. Knowledge of the preoperative imaging and localization studies did guide the exploration in that a general exploration was performed on all patients, but specific areas were focused based on preoperative imaging. Any suspicious finding by palpation was noted, and subsequently following ultrasound was excised or resected for pathologic analysis.

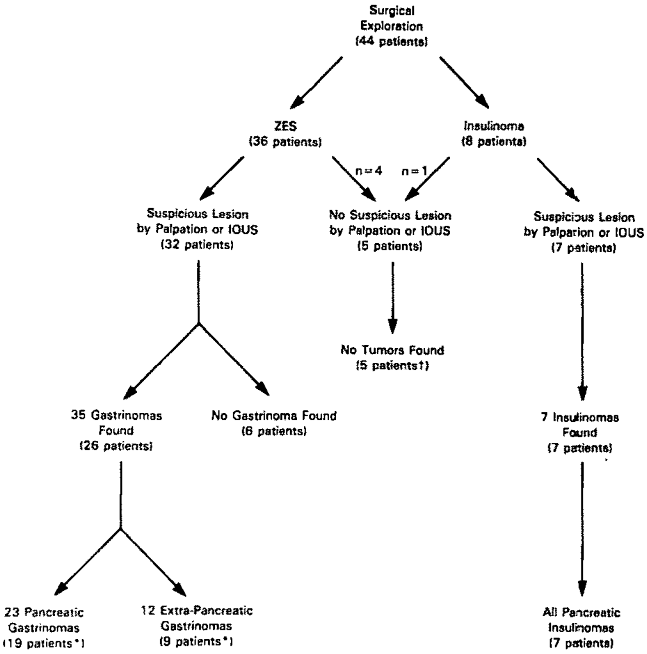

Surgical Exploration (44 patients)
ZES (36 patients)
Insulinoma (8 patients)
n=4
n=1
Suspicious Lesion by Palpation or IOUS (32 patients)
No Suspicious Lesion by Palpation or IOUS (5 patients)
Suspicious Lesion by Palparion or IOUS (7 patients)
No Tumors Found (5 patients†)
35 Gastrinomas Found (26 patients)
No Gastrinoma Found (6 patients)
7 Insulinomas Found (7 patients)
23 Pancreatic Gastrinomas (19 patients*)
12 Extra-Pancreatic Gastrinomas (9 patients*)
All Pancreatic Insulinomas (7 patients)

FIG. 1. Flow diagram describing the number of patients in the study divided into tumor types, suspicious operative findings, and the numbers of tumors proven pathologically in different patients. †Five patients were excluded from analysis because no tumors were found and no suspicious operative findings were identified by palpation or IOUS. *Two patients had gastrinomas found both within and outside of the pancreas.

After full operative exposure and completion of manual palpation, realtime IOUS was performed using a Diasonics ultrasound scanner (model DRF 1; Diasonics Inc., Milipitas, CA) and a 10 MHz mechanical-sectoring transducer. Realtime studies were recorded on videotape. The transducer was inserted into a long, sterile, plastic sleeve containing methylcellulose gel at the distal tip. The abdominal cavity was filled with warm saline to provide additional acoustic coupling. The pancreas was scanned by passing the probe from the pancreatic head across the body to the tail, visualizing the pancreas in the longitudinal (sagittal) scanning plane. Several parallel passes were necessary for complete examination of the pancreas. Next, the pancreatic head, uncinate process, and duodenum were manually manipulated for optimal exposure and ultrasound visualization. All suspicious findings from palpation were carefully delineated by IOUS examination. The IOUS study was considered positive for islet cell tumor if a sonolucent mass lesion could be detected in both transverse and longitudinal imaging planes. After completion of the IOUS examination, the pancreas and peripancreatic tissues were again carefully palpated. Duodenal nodules were better exposed by opening the duodenal wall. Any suspicious pancreatic, stomach, duodenal, bowel, peripancreatic nodule, or lymph node, whether detected by palpation or intraoperative ultrasound, was biopsied. In the bowel or stomach wall, a suspected tumor was excised with a full thickness rim of normal tissue around the tumor. In the pancreatic head or adjacent lymph node areas, suspected tumors were enucleated. In the pancreatic body and tail, a pancreatic resection or enucleation was performed dependent on the size and appearance of the tumor. Lesions thought to be malignant were resected by subtotal or distal pancreatectomy and splenectomy.

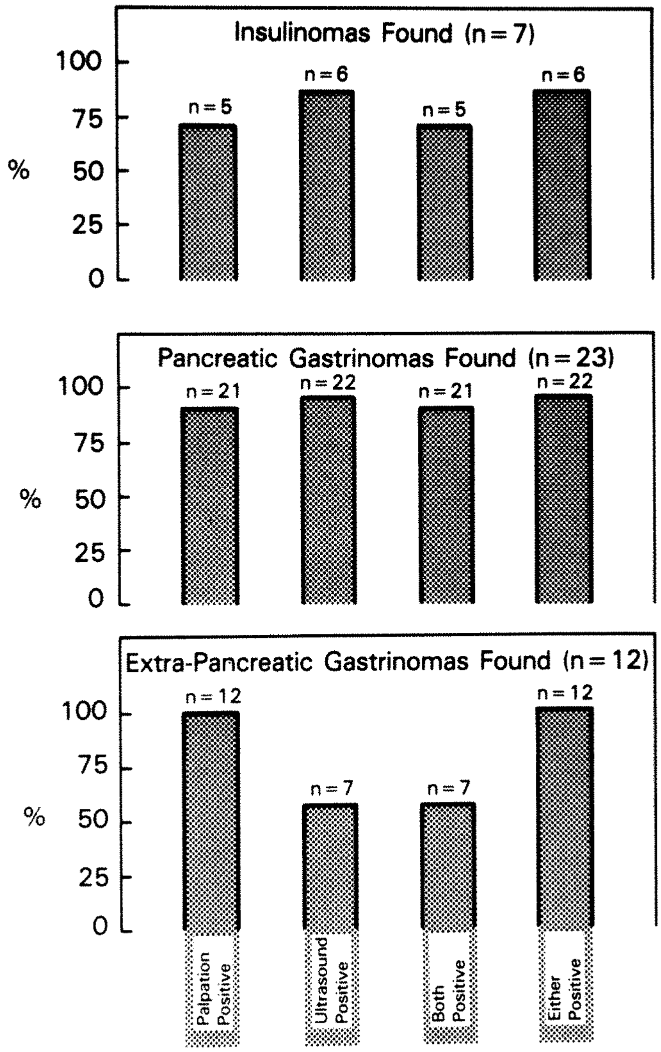


FIG. 2. Percentages for true-positives of operative localization methods including palpation alone, ultrasound alone, both combined and either positive in finding pancreatic insulinomas, pancreatic gastrinomas, and extrapancreatic gastrinomas. Statistically, both operative methods are comparable in finding pancreatic insulinomas and gastrinomas. Palpation is significantly better at localizing extrapancreatic gastrinomas than ultrasound ($p < 0.01$).

Results of intraoperative localization procedures (palpation and ultrasound) were compared to the final surgical, pathologic, and diagnostic proof of islet cell tumor. A decision analysis was performed on the results of intraoperative localization procedures using a method described by Weinstein and Fineberg.[14] After the pathologic results of the operation were known, manual palpation, or IOUS, were rated as true-positive, true-negative, false-positive, or false-negative. A true-positive result was defined as one in which an islet cell tumor was found in the exact location suggested by the intraoperative procedure. A true-negative result was one in which one localization maneuver suggested that no tumor was present in a given location, while the other localization maneuver suggested that tumor was present and no tumor was identified on biopsy. False-positive results were defined as erroneous tumor locations indicated by intraoperative maneuvers. False-negative results were defined as failure to image or palpate a tumor that was subsequently found. Sensitivity of the two methods was calculated by dividing true-positive results by the sum of true-positive and false-positive results. Sensitivity percentages were compared statistically by the Fischer's exact test. Size of tumors detected and not detected by IOUS were compared by unpaired t-test.

Results

Forty-four patients entered this study. Thirty-six patients had the diagnosis of ZES and eight patients had the diagnosis of insulinoma. All patients underwent exploratory laparotomy for tumor resection. Five patients (one insulinoma, four ZES) were excluded from this analysis because intraoperative localization procedures produced no suspicious findings and islet cell tumors were not found (Fig. 1). Suspicious lesions were identified by palpation and/or operative ultrasound in 39 patients (32 ZES, seven insulinoma) who formed the basis of the present analysis. Seven insulinomas (proven pathologically) were detected in the seven patients with a clinical diagnosis of insulinoma, and all tumors were within the pancreas. Six patients with ZES who had suspicious lesions by operative ultrasound and/or palpation had no gastrinomas proven pathologically. In 26 patients with ZES, 35 gastrinomas were proven pathologically. In 19 patients with ZES, 23 gastrinomas were found within the pancreas and in 9 patients, 12 gastrinomas were extrapancreatic. Two patients with ZES had gastrinomas both within and outside of the pancreas (Fig. 1).

TABLE 1. *Palpation* versus *IOUS in Localizing Insulinomas and Gastrinomas*

	Insulinoma (7)		Gastrinoma (35)	
	Palpation	IOUS	Palpation	IOUS
True-positive	5	6	33	29
True-negative	0	1	5	3
False-positive	1	0	9	11
False-negative	2	1	2	6
Sensitivity* (%)	71	86	94	83

Values in parentheses are the total no. of tumors proven pathologically.

* Sensitivity of palpation *vs.* IOUS at localizing gastrinomas or insulinomas is not significantly different.

Palpation Versus *IOUS to Localize Islet Cell Tumors*

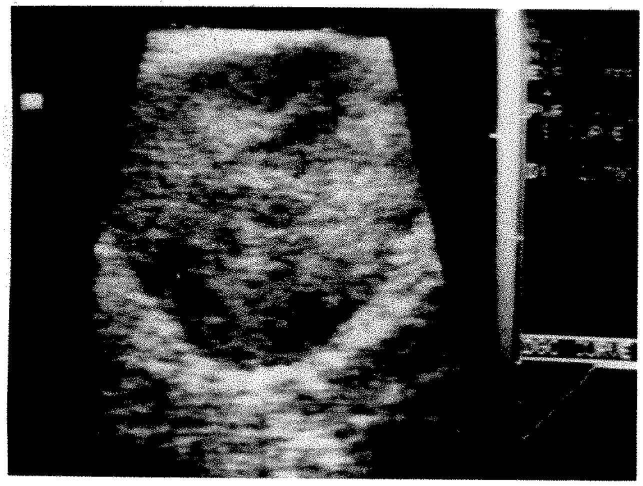
IOUS correctly identified six of seven insulinomas, while palpation only identified five (Fig. 2, Table 1). One insulinoma was not detected by palpation or IOUS and was found following a blind distal pancreatectomy in a patient with a selective insulin gradient in the distal pancreas detected by PVS. The IOUS appearance of most islet cell tumors typically demonstrated a sonolucent mass lesion with discrete echogenic borders (Fig. 3) as described previously.[8-10] Palpation correctly identified 33 of 35 gastrinomas while IOUS only identified 29 (Table 1, Fig. 2). Both methods were equal (sensitivity) in their ability to localize insulinomas and gastrinomas (Table 1). Each method individually was similar to either method alone or both methods together in ability to detect insulinomas or pancreatic gastrinomas (Table 2, Fig. 2). Extrapancreatic gastrinomas were identified better by palpation (12 of 12, sensitivity = 100%) than IOUS (7 of 12, sensitivity = 58%) ($p < 0.01$) (Fig. 2, Table 2).

TABLE 2. *Palpation* versus *IOUS in Localizing Pancreatic and Extrapancreatic Gastrinomas*

	Pancreatic Gastrinoma (23)		Extrapancreatic Gastrinoma (12)	
	Palpation	IOUS	Palpation	IOUS
True-positive	21	22	12	7
True-negative	5	1	0	2
False-positive	4	8	5	3
False-negative	2	1	0	5
Sensitivity (%)	91	95	100	58*

Values in parentheses are the total no. of tumors proven pathologically.

* Palpation is more sensitive than IOUS at localizing extrapancreatic gastrinomas ($p < 0.01$), but the two methods are equal at localizing pancreatic gastrinomas.



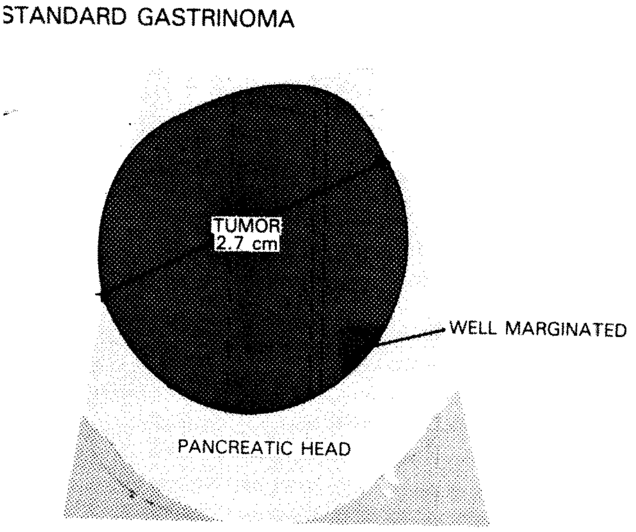


FIG. 3. Operative sonographic appearance of a typical islet cell tumor. The tumor is sonolucent compared to the surrounding pancreas, which is more echogenic. The margin of the tumor and the pancreas is discrete with an echogenic rim around the entire tumor. This appearance is consistent with a benign islet cell neoplasm.

When one combines the pancreatic gastrinomas and insulinomas, 30 islet cell tumors were found within the pancreas. Palpation had 26 true positive findings and IOUS had 28 (Table 3). Sensitivity for palpation (87%) was again similar to sensitivity for IOUS (93%).

False-positive and False-negative Results

False-positive and false-negative localization occurred with both palpation and IOUS for both insulinomas and gastrinomas (Table 1). Whereas the overall rate of either false-positive or false-negative results for palpation and IOUS was not significantly different (Table 3) ($p > 0.1$), analysis of the false-positive cases (Table 4) or false-negative cases (Table 5) demonstrates a number of important features. The duodenum is a common location for gastrinoma, but it was also a common location for ectopic pancreas (three cases) (Table 4), which was identified as a positive tumor in each case by palpation and in one case by IOUS. A 0.5–1.0 cm mass in the pancreatic head area was identified as a gastrinoma in four cases by IOUS and confirmed in one case by palpation, but was found to be a normal intrapancreatic lymph node in the four patients (Table 4). Normal pancreas, scar tissue from previous ulcer disease, and dilated pancreatic ducts were also sources of false-positives (Table 4).

An analysis of the false-negative responses demonstrates that both the size and location of the gastrinoma were important variables (Table 5). The size of the gastrinomas missed by IOUS was significantly smaller than

TABLE 3. *Palpation* versus *IOUS in to Localizing Intrapancreatic Islet Cell Tumors*

	Intrapancreatic Islet Cell Tumors (gastrinomas and insulinomas) (30)	
	Palpation	IOUS
True-positive	26	28
True-negative	5	2
False-positive	5	8
False-negative	4	2
Sensitivity (%)	87	93*

Value in parentheses is the total no. of tumors proven pathologically.

* There is no significant difference between IOUS and palpation.

the size of the gastrinomas correctly identified (0.4 ± 0.05 *vs.* 1.9 ± 0.4 cm, $p < 0.05$, Table 5). Location was important because extrapancreatic gastrinomas were more frequently missed by IOUS than pancreatic gastrinomas (Table 5). Specifically, 1 of 23 pancreatic gastrinomas and 5 of 12 extrapancreatic gastrinomas were missed by IOUS ($p < 0.01$, Table 5). Of the five extrapancreatic gastrinomas missed by IOUS, all five were in the duodenum (Table 5).

Surgical Impact of IOUS

IOUS affected the intraoperative decision process or the ability to find an islet cell tumor in 5 of 44 patients (11%). In three patients (two ZES, one insulinoma), IOUS correctly suggested a malignant gastrinoma that was not obvious by palpation (patients 1, 2, and 5, Table 6). In these patients IOUS demonstrated indistinct margins of the tumor with extension into adjacent pancreas (Fig. 4) and obliteration of the pancreatic duct (Fig. 5). Pancreatic resections were performed based on IOUS findings (Table 6). In two other patients (patients 3 and 4, Table 6) (one with gastrinoma and one with insulinoma), tumors would not have been identified without IOUS. One patient with occult insulinoma in the pancreatic head, which was identified only by IOUS, had been described in detail previously.[10] The other patient with ZES was similar. Portal venous sampling for gastrin suggested that a gastrinoma was located in the pancreatic head region. Careful operative palpation revealed no tumor and a Whipple pancreaticoduodenectomy was not believed to be a reasonable surgical option. Operative ultrasonography revealed a 1-cm sonolucent mass in the posterior head of the pancreas near the common bile duct. The gastrinoma was enucleated with intraoperative ultrasound guidance, and a pancreatic resection was not done. Follow-up of all five patients indicates that each has no evidence of recurrent islet cell tumor.

Discussion

Although IOUS is a recent addition to surgical practice, it is clear that islet cell tumors of the pancreas can be detected intraoperatively by realtime B-mode ultrasonography.[15] The sonographic appearance of islet cell tumors at operation is identical to that described for these tumors detected by ultrasound preoperatively (Fig. 3).[16] The difference in echogenicity between the tumor (typically low echo amplitude) and the pancreas (high echo amplitude) accounts for the visibility of the tumor.[10] Preliminary reports suggest that IOUS has great potential in localizing small islet cell neoplasms[8-10]; yet IOUS is expensive (the equipment in the

TABLE 4. *False-positive Results for Gastrinoma Patients with Palpation and/or IOUS*

Palpation (N = 10)	IOUS (N = 11)	Pathology
2-cm pancreatic tail nodule	2-cm sonolucent lesion	Normal pancreas (no tumor)
Nodule in pyloric wall	Sonolucent 4-mm nodule pyloric wall	Ectopic pancreas (no tumor)
Nodule in duodenal wall	Negative	Ectopic pancreas (no tumor)
Nodule in jejunal wall	Sonolucent 5-mm nodule	Scar from prior ulcer
Negative	Sonolucent 5-mm lesion pancreatic head	Normal lymph node within pancreatic head
Nodule in duodenal wall	Sonolucent nodule duodenal wall	Lipoma duodenal wall
Nodule in posterior pancreatic head	Sonolucent nodule in posterior pancreatic head	Lymph node
Negative	Sonolucent nodule in pancreatic head	Scar tissue with pancreas
Negative	1-cm sonolucent nodule within pancreatic head	Lymph node
Negative	Sonolucent nodule in pancreatic head	Normal pancreas no tumor seen
Nodule in pancreatic tail	Negative	Normal pancreas
Negative	8-mm sonolucent lesion in pancreatic head	Lymph node
0.5-cm nodule in pancreatic body	Sonolucent lesion in pancreatic body	Dilated ectopic pancreatic duct
Nodule in duodenal wall	Negative	Ectopic pancreas
Nodule body of pancreas	Negative	Normal pancreas

TABLE 5. *IOUS Result as a Function of Gastrinoma Size and Location*

			Location					
			Pancreas (N = 23)			Extrapancreatic (N = 12)		
IOUS Result	Gastrinomas Found	Diameter* (cm)	Head	Body	Tail	Duodenal Wall	Jejunal Wall	Other
Positive	29	1.9 ± .4 (0.4–10.0)	14	3	5	4	2	1 (ovary)
Negative	6	0.4 ± .05† (0.2–0.6)	—	—	1	5	—	—
Total	35	—	14	3	6	9	2	1

* Value for diameter is mean ± SEM; other numbers are total number.

† Significantly less than diameter of positive result ($p < 0.05$).

present study costs $80,000), requires expertise, and adds time to the operation. Until the present study, no prospective evaluation of IOUS compared to traditional operative techniques such as palpation had been done. The present study demonstrates no overall difference between palpation and ultrasound in the ability to intraoperatively localize pancreatic islet cell tumors; however, it demonstrates that in 11% of patients IOUS provides information not provided by palpation that affects surgical management. For localizing extrapancreatic islet cell tumors, palpation is significantly better than IOUS.

The observed equality between palpation and IOUS in the ability to find pancreatic islet cell tumors was unexpected in light of a number of preliminary reports[8–10,15,17] that IOUS might frequently localize islet

TABLE 6. *IOUS Affected Surgical Decision-making or Ability to Find Islet Cell Tumor*

Patient (N = 5) (11%)	Diagnosis	Impression Postpalpation	IOUS Finding	Surgical Procedure	Pathologic Analysis	Follow-up
1	ZES	Well-defined 2-cm tumor pancreatic tail	2-cm tumor with indistinct margins and extension outside pancreatic tail	Distal pancreatectomy splenectomy	Malignant gastrinoma with vascular invasion and extension outside pancreas into fat	Cured at 6 months
2	ZES	Well-defined 2-cm tumor midpancreatic body	Same 2-cm tumor with invasion into pancreas and extension outside pancreas	Subtotal pancreatectomy splenectomy	Malignant gastrinoma with extension into peripancreatic fat and vascular invasion	Cured at 6 months
3	ZES	No tumor palpable	1-cm well-demarcated tumor in posterior pancreatic head near common duct	Enucleation	1-cm gastrinoma from pancreatic head	Cured at 6 months
4	Insulinoma	No tumor palpable	7-mm well-demarcated tumor in pancreatic head	Enucleation	7-mm insulinoma from pancreatic head	Cured at 3 years
5	Insulinoma	Well-defined 1.5-cm tumor midpancreatic body	1.5-cm tumor without distinct margins and extension into adjacent pancreas	Subtotal pancreatectomy splenectomy	2.0-cm insulinoma with vascular invasion and invasion into adjacent pancreas	Cured at 2 years

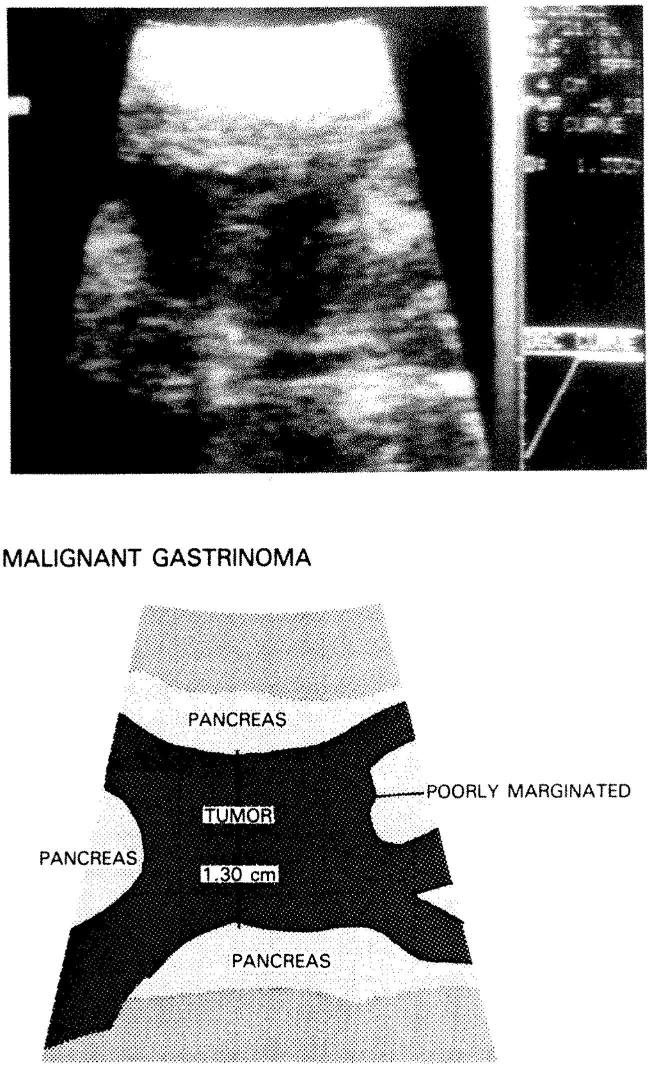


FIG. 4. Operative sonographic appearance of an islet cell tumor that was subsequently resected and proven to have malignant features pathologically. The tumor was sonolucent compared to the echogenic surrounding pancreas, but the border of the tumor was not clearly marginated and there was extension into surrounding pancreas. This sonographic appearance was consistent with a malignant islet cell neoplasm.

cell tumors not identified by palpation. A number of factors could contribute to our results. The difference in our results from those suggested in preliminary reports was unlikely to be due to a difference in expertise or the IOUS equipment used. In the present study, state-of-the-art IOUS equipment with a 10 MHz transducer was used to give the greatest possible resolution, whereas in earlier studies either 5 or 7.5 MHz[9,15] transducers were used. Although a learning curve exists for IOUS, at all operations an untrasonographer with extensive experience with ultrasound identification of islet cell tumors was present.[16] Furthermore, the sensitivity of detecting all pancreatic islet cell tumors in the present study was 93% (Table 3), which agrees closely with the sensitivity of 86% recently reported by another group with considerable expertise with IOUS localization of insulinomas.[17] It could be argued that the extensive preoperative localization studies (imaging studies, PVS), in fact, contributed disproportionally in increasing the sensitivity of palpation, which was 87% in the present study. This cannot be excluded; however, this information was available for both palpation and IOUS and should have affected the result from each procedure equally. Last, it cannot be excluded that in other centers with less experience with islet cell tumors, that IOUS may, in fact, contribute significantly more than found in the present

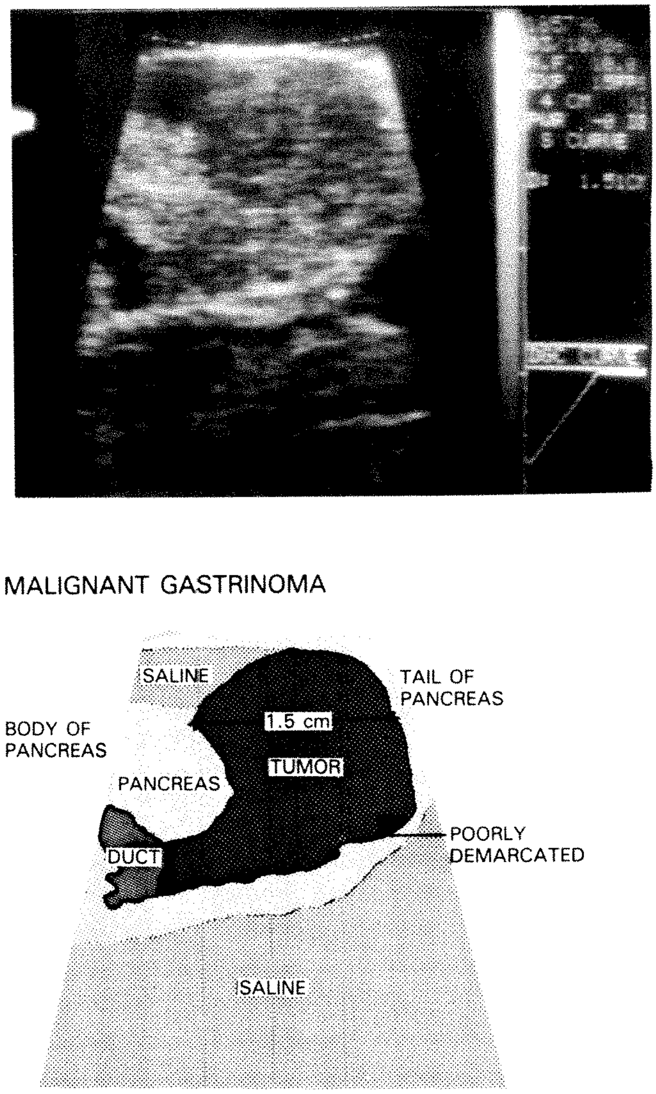


FIG. 5. Operative sonographic appearance of an islet cell tumor that was subsequently resected and proven to have malignant features pathologically. Again, the border of the pancreas and the tumor was not clearly marginated and there was total blockage of the pancreatic duct by direct invasion. This sonographic appearance was consistent with a malignant islet cell neoplasm.

study. In the present study, all patients have extensive exploration with kocherization of the duodenum, complete mobilization of the pancreatic tail, and frequently opening the duodenum even though more than one third have had previous upper abdominal surgery. This is possible because of the ability to control gastric acid hypersecretion at the time of surgery, and this allows for extensive palpation of all areas; whereas in centers with less experience, either because of adhesions from previous surgery or the inability to control hypersecretion of gastric acid, a thorough exploration may not be done, in which case IOUS may be even more valuable. Furthermore, the operating surgeon in the present study has had significant experience recognizing and palpating islet cell tumors that may have contributed to the high sensitivity of palpation.

In a technologic age, it is tempting to discount traditional operative methods like visualization and palpation in favor of expensive high technology equipment that can penetrate into structures in a noninvasive manner. However, our data clearly indicate that there are no significant differences between the two methods in detecting pancreatic islet cell tumors and that cost-effective palpation is significantly better at detecting extrapancreatic tumors. The results suggest that basic time-honored operative techniques such as palpation and visualization should not be replaced by IOUS in the search for islet cell tumors especially ones that are extrapancreatic in location. However, the results also indicate that IOUS does contribute in a fraction of patients, and in fact, is complementary to palpation.

Analysis of the false-negative and false-positive results for both palpation and IOUS provide a number of important insights. Analysis demonstrates that both the size of the islet cell tumor and location are important determinants of the false-negative rate for IOUS. Specifically, IOUS is less likely to detect an extrapancreatic gastrinoma than a pancreatic gastrinoma or insulinoma, whereas there is no difference for palpation. Furthermore, the size of gastrinomas detected with IOUS is significantly different from those not detected. Detection of sonolucent islet cell tumors by IOUS is clearer against a homogeneous echogenic background such as the pancreas than a mixed (gas-liquid-solid) background like the bowel. Small tumors (0.2–0.6 cm) in the duodenum have a higher likelihood of not being imaged, not because the 10 MHz transducer lacks resolution, but because resolution depends on the homogeneity of the background. Because in some series up to 50% of gastrinomas are extrapancreatic,[4,18,19] these results suggest that IOUS may be generally more helpful in localizing insulinomas than gastrinomas. Another difficult region to accurately image is the pancreatic tail because it is difficult to position the transducer under the left costal margin. This technical problem may be solved by mobilizing the tail of the pancreas and the spleen out of the retroperitoneum for examination, or by using a right angle high-resolution transducer (which was not available during this study). However, routine mobilization of the spleen in this manner may increase the risk of splenic injury and splenectomy. Finally, ultrasound detected some nonpalpable small false-positive images in the pancreatic head that appeared as sonolucent mass lesions similar to islet cell tumors. These lesions are normal lymph nodes within the pancreas. False-positives and false-negatives limit the present utility of IOUS and with more observer experience may be partially resolved.

A newly described advantage of IOUS is that it appears to differentiate malignant islet cell tumors from benign tumors. Benign tumors are very well demarcated with distinct hyperechoic borders (Fig. 3). Three tumors had indistinct borders, suggesting invasion into adjacent pancreas and pancreatic duct (Fig. 4 and 5), presumptive signs of malignancy. One tumor (Fig. 5) was small with ductal invasion; thus, size alone does not predict malignant potential. These tumors were resected based on IOUS results, and were found to have malignant features on pathologic analysis. Further instances and observations from other groups will be necessary to see how reliable the ultrasonic appearance of tumors predicts invasiveness and malignancy. Because up to 60–90% of gastrinomas are malignant,[12,19] whereas up to 80–90% of insulinomas are benign,[11] if, in fact, with greater experience it can be verified that IOUS can identify invasiveness, this suggests that IOUS will be more useful with gastrinomas than insulinomas to assess malignancy.

The most important consideration with any new technique is outcome. Operative sonography had clear impact on the final outcome of five patients (11%) in this study. It enabled the surgeon to find and remove two tumors that would not have been found or removed without it. It advised the surgeon to resect (instead of enucleate) three tumors with pathologic evidence of malignant invasion. All five patients in whom IOUS altered the surgical procedure are cured, albeit with short follow-up. The observation that IOUS can improve the ability of an experienced surgeon to find some nonpalpable islet cell tumors and can provide additional valuable information about invasiveness, allows us to make a strong recommendation for its use during explorations for islet cell neoplasms.

This study combined with other reports[17] indicates that IOUS is useful during abdominal explorations for pancreatic islet cell tumors. A sonolucent pancreatic mass imaged by IOUS should not be ignored because in some instances, pancreatic islet cell neoplasms will be detected that may not be palpable or visible. The appearance of islet cell tumors and their interaction with adjacent pancreas and structures can provide evidence for malignant potential and rational resection.

In conclusion, even though palpation was the single best localization method because of equal sensitivity within the pancreas and better sensitivity outside the pancreas, the present results demonstrate that, in fact, palpation and IOUS are complementary because IOUS detects some tumors that are not palpated and can provide information concerning malignant potential not detected by palpation.

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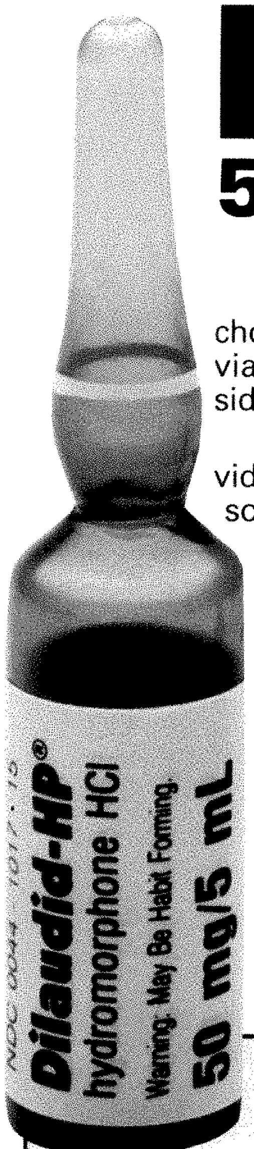

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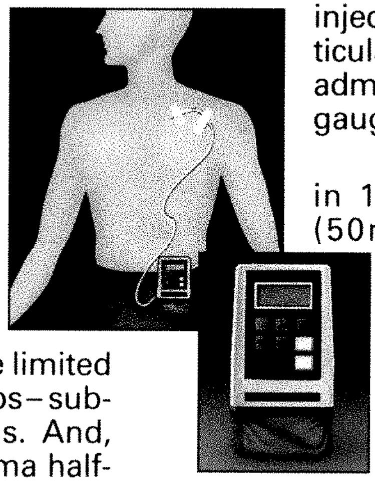

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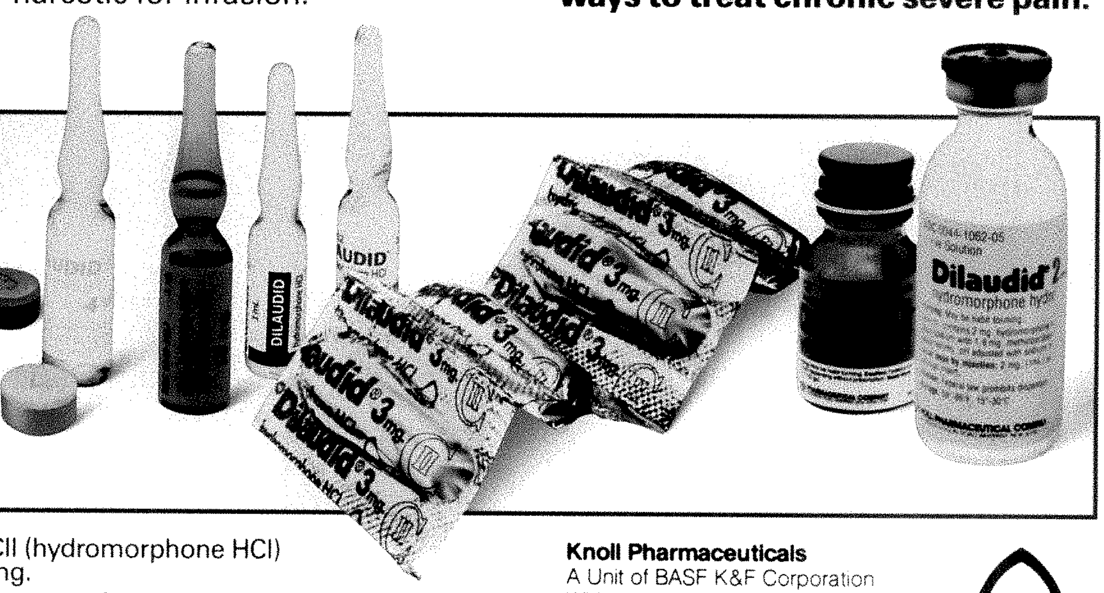

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The Effect of Somatostatin on Experimental Intestinal Obstruction

SEAN J. MULVIHILL, M.D.,* THEODORE N. PAPPAS, M.D.,‡ ERIC W. FONKALSRUD, M.D.,† and HAILE T. DEBAS, M.D.*

The effect of somatostatin (SS-14) was tested in an anesthetized rabbit model of closed-loop ileal obstruction. Experimental groups included (1) immediate treatment (N = 6) receiving SS-14 2,000 pmol × kg^{-1} × h^{-1} intravenously (I.V.) beginning at the time of ileal obstruction, (2) delayed treatment (N = 5) receiving SS-14 beginning 6 hours following ileal obstruction, and (3) control (N = 6) receiving only hydration. After 24 hours, all rabbits were killed. Significantly decreased intestinal luminal volume and sodium and potassium output was observed with both immediate and delayed SS-14 treatment when compared to control. Additionally, the gross and microscopic pathologic features of intestinal distension, inflammation, and necrosis seen in control rabbits were absent in rabbits treated with SS-14. The known broad spectrum of physiologic activity of SS-14 on the gastrointestinal tract appeared beneficial in this rabbit model of intestinal obstruction.

From the Departments of Surgery, University of California (San Francisco and Los Angeles†) and Peter Bent Brigham Hospital, Boston, Massachusetts‡*

SMALL INTESTINAL OBSTRUCTION is a common problem in surgical practice with significant morbidity and mortality rates. Historically, the recognition of hypovolemia as the major cause of death in intestinal obstruction by McCallum and others in the early 1900s, and the development of nasoenteric suction tubes for intestinal decompression by Wangensteen in the 1930s, represented major advances in the treatment of patients with intestinal obstruction. As a consequence, mortality rates decreased from 60–10% by 1955.[1] Since that time, however, few other improvements in management have occurred, and certain patients, particularly those with recurrent partial obstruction, obstruction in the early postoperative period, and obstruction associated with malignancy, present vexing clinical problems. The major morbidity rate of intestinal obstruction is still related to excessive distension leading to strangulation and bowel necrosis. There currently is no treatment directed at the known abnormal secretory patterns of the obstructed intestine.

Somatostatin (SS-14), a cyclic tetradecapeptide, was first isolated in 1973 by Brazeau et al.[2] and subsequently found to have a broad spectrum of gastrointestinal activity, including inhibition of certain hormones and inhibition of secretory and motor functions of the intestine.[3] Numerous anecdotal reports indicate that these actions of SS-14 and its analogues may be exploited to clinical advantage.[4] We hypothesized that the effects of SS-14 on intestinal ion and water transport might reduce the distension caused by mechanical obstruction.

Materials and Methods

Seventeen New Zealand rabbits (mean weight: 3.0 kg) were anesthetized with I.V. urethane (1000 mg × kg^{-1}). Hydration was maintained with I.V. infusion of Ringer's lactate (4.0 mL × kg^{-1} × h^{-1}) for the duration of the study. In each, a laparotomy was performed and a uniform 25-cm closed loop obstruction was created with ligatures in the distal ileum. This procedure had the effect of creating a simple obstruction of the proximal intestine, in addition to the ileal closed loop. Rabbits were divided randomly into three groups: (1) immediate treatment (N = 6), (2) delayed treatment (N = 5), and (3) control (N = 6). Rabbits in the immediate treatment group received SS-14 (2000 pmol × kg^{-1} × h^{-1}) in 0.1% bovine serum albumin carrier at 6.6 mL × h^{-1} I.V. beginning at the time of obstruction. Rabbits in the delayed treatment group received the same dose of SS-14 infusion but beginning 6 hours following the creation of

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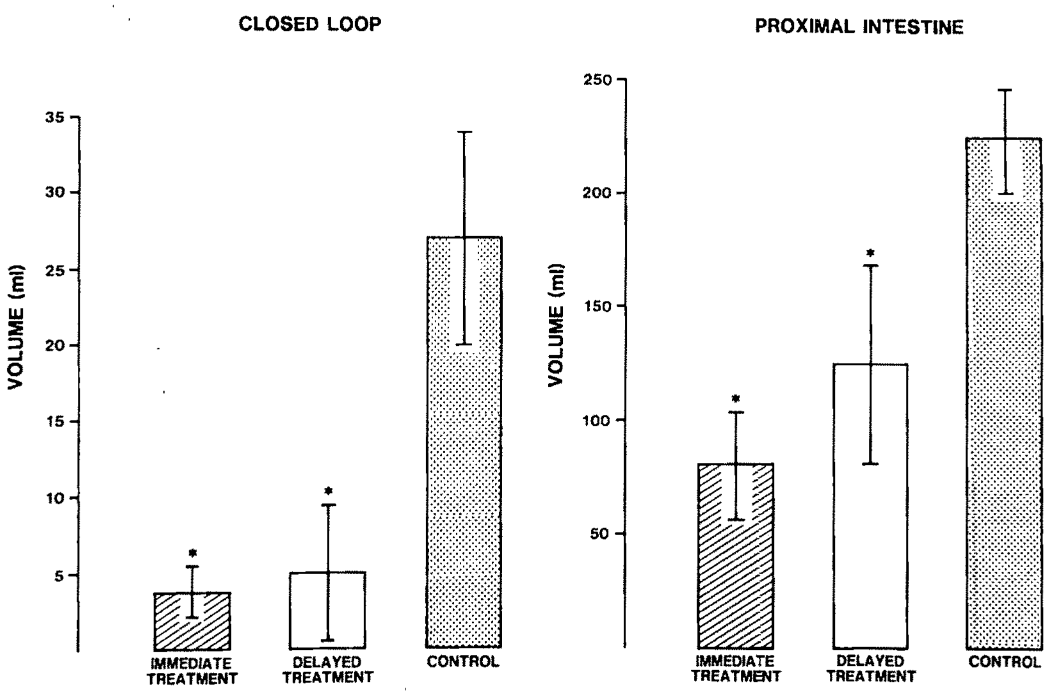

FIG. 1. Effect of immediate and delayed treatment with SS-14 of small intestinal obstruction in closed-loop and proximal segments on intestinal luminal volume. *p < 0.05 compared to control.

the obstruction. This was done to simulate the clinical situation in which patients present several hours after the onset of their obstruction. Control rabbits received the carrier alone at the same rate of infusion.

After 24 hours, the rabbits were killed with an overdose of pentobarbital, and the intestines examined. An observer who did not know to which treatment group the rabbits belonged calculated a gross pathologic score based on the presence or absence of bowel distension, edema, erythema, cyanosis, adhesions, necrosis, perforation, and free peritoneal fluid (0 = normal score; 10 = maximal score). Luminal contents of the obstructed intestine were measured and aliquots saved for analysis of sodium and potassium by flame photometry. Samples of obstructed intestine were preserved in formalin, sectioned and stained with hematoxylin and eosin, and examined microscopically for the presence or absence of inflammatory infiltrates, hemorrhage, and mucosal necrosis. With these criteria, a microscopic pathology score was assigned (0 = normal score; 3 = maximal score).

SS-14 (Sigma Chemical Company, St. Louis) was mixed freshly from the powder in carrier solution for each experiment. The infusate solutions were kept on ice and infused by Harvard peristaltic pumps at a constant rate. No rabbits vomited, and all survived the 24-hour study period. Since the animals were kept anesthetized for the entire 24-hour period, they experienced no pain. This study was performed in accordance with the guidelines of the National Research Council for the care and use of laboratory animals.

Statistical analysis was performed utilizing Student's t-test for unpaired values. A p value of less than 0.05 was considered significant. Throughout, the data is given as mean ± SEM.

Results

SS-14 treatment had a profound effect on luminal volume in the obstructed small intestine, both in the closed loop and in the proximal portions. Control rabbits had a mean luminal volume of 26.9 ± 7.0 mL in the closed-loop segment, whereas rabbits receiving immediate SS-14 treatment had only 3.7 ± 1.7 mL, representing a sevenfold reduction in fluid volume. Rabbits receiving delayed treatment with SS-14 had a mean luminal volume of 4.9 ± 4.8 mL. In the small intestine proximal to the closed-loop segment, significant reductions in luminal volume were also seen with immediate and delayed SS-14 treatment (224 ± 22 mL control *vs.* 80 ± 24 mL immediate treatment and 124 ± 43 mL delayed treatment). These data are summarized in Figure 1.

Although luminal sodium concentration was unchanged in the treated and in the control groups (148 ± 4 mmol $\times$ L^{-1} *vs.* 147 ± 5 mmol $\times$ L^{-1}), there was a significant reduction in luminal sodium output in both the immediate and the delayed treatment groups when compared to control (Fig. 2). Mean luminal sodium output in the closed-loop segments was 3.8 ± 0.1 mmol in the control group compared with 0.5 ± 0.2 mmol in the immediate treatment group and 0.8 ± 0.8 mmol in the delayed treatment group. Similarly, significant re-

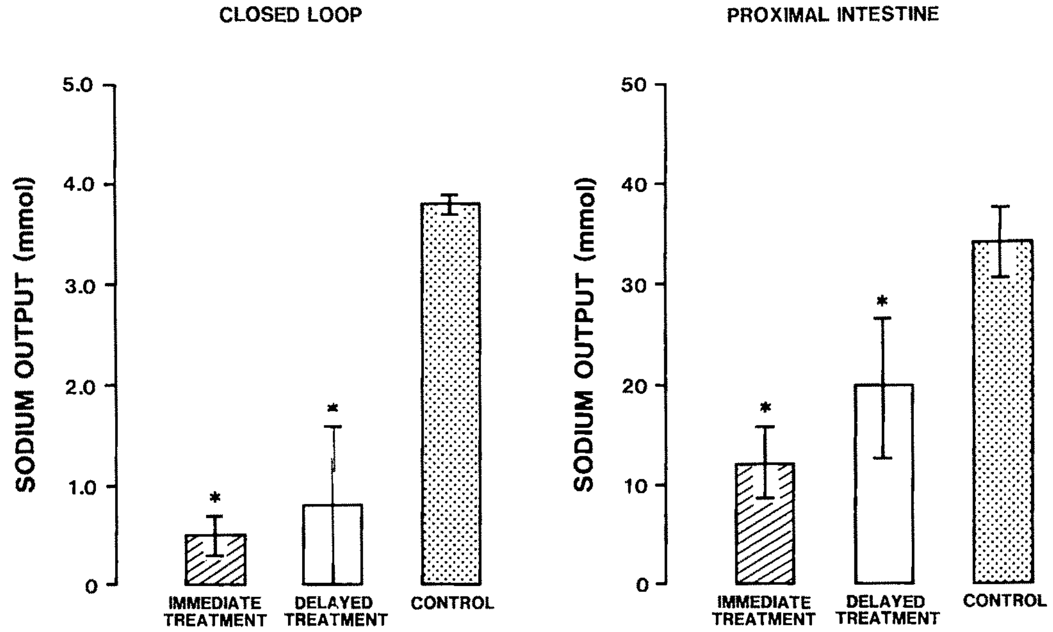

FIG. 2. Luminal sodium output in obstructed rabbit small intestine with and without treatment with SS-14. *p < 0.05 compared to control.

ductions in luminal sodium output occurred in the intestine proximal to the closed-loop segments with SS-14 treatment (33.9 ± 3.5 mmol control *vs.* 12.2 ± 3.6 mmol immediate treatment and 19.7 ± 7.1 mmol delayed treatment).

SS-14 treatment resulted in significantly increased luminal potassium concentration but decreased potassium output in the proximal obstructed intestine (Table 1). In the closed-loop segments, there were no significant differences in luminal potassium concentration. SS-14 treatment, however, resulted in significant decreases in luminal potassium output in both the immediate and delayed treatment groups when compared to control.

SS-14 treatment also resulted in dramatic differences in the gross appearance of the obstructed intestine compared to control. In the closed-loop segments, control rabbits had a mean gross pathologic score of 5.3 ± 1.3, with three rabbits having localized areas of necrosis. Closed-loop segments in rabbits treated with SS-14 had essentially none of the aforementioned changes, with mean scores of 0.3 ± 0.2 (immediate treatment) and 0.6 ± 0.6 (delayed treatment). Although the proximal intestine was not as severely affected as the closed-loop segments in control rabbits (mean score: 3.8 ± 0.9), significant improvements were still observed with SS-14 treatment (immediate treatment: 0.7 ± 0.2; delayed treatment: 1.2 ± 0.5). These data are shown in Figure 3.

At microscopic examination, the above gross findings were confirmed in the closed-loop segments. Figure 4 depicts the microscopic pathologic scores from closed-loop segments in control rabbits (2.3 ± 0.3) compared to immediate treatment (0.3 ± 0.2) and delayed treatment (0.4 ± 0.2) rabbits. Extensive mucosal necrosis and intramural hemorrhage and inflammatory infiltrates were seen in closed-loop segments from control rabbits, findings that were absent in the group treated with SS-14. Representative sections are shown for comparison in Figure 5. No significant histopathologic changes were seen in the proximal intestine in any of the groups.

Discussion

In the face of unremitting mechanical obstruction, progressive intestinal distension leads to vascular com-

TABLE 1. *Luminal Potassium Concentration and Output in Segments of Obstructed Small Intestine*

	Closed-loop Segment		Proximal Segment	
	Potassium Concentration (mmol × L^{-1})	Potassium Output (mmol)	Potassium Concentration (mmol × L^{-1})	Potassium Output (mmol)
Immediate treatment	8.1 ± 2.7	0.03 ± 0.01*	10.8 ± 2.0*	0.72 ± 0.19*
Delayed treatment	8.2 ± 8.2	0.04 ± 0.04*	9.0 ± 1.6*	1.05 ± 0.27
Control	4.9 ± 0.5	0.13 ± 0.01	5.7 ± 0.6	1.28 ± 0.13

* $p < 0.05$.

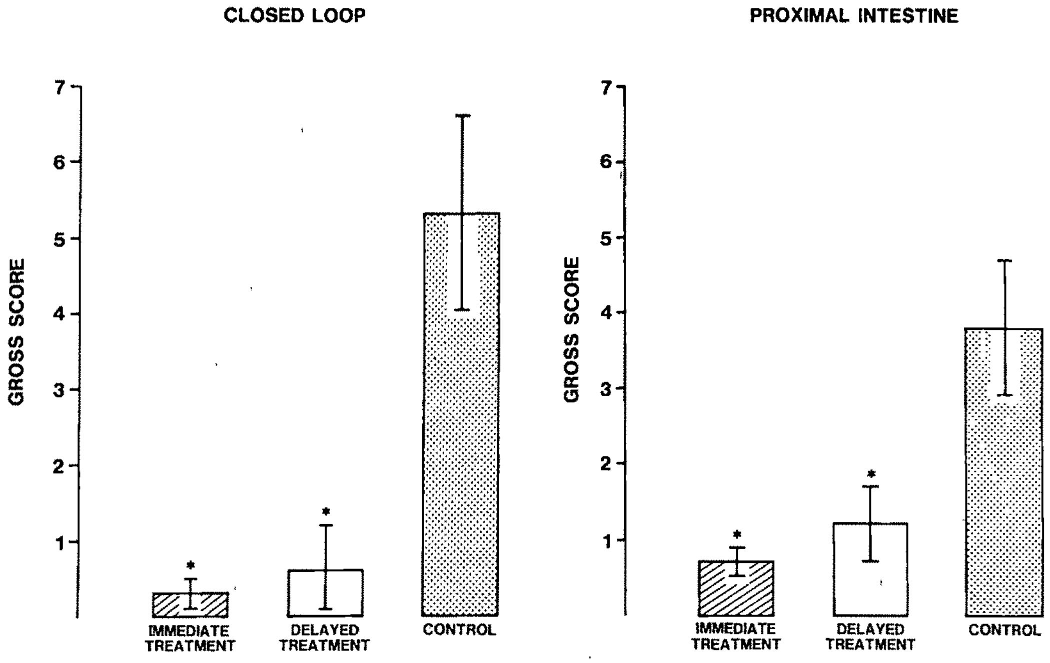

FIG. 3. Gross pathologic score of obstructed intestine with and without SS-14 treatment. $*p < 0.05$ compared to control.

promise, ischemia, and necrosis. At least three factors contribute to intestinal distension in this situation: (1) accumulation of gastric, pancreatic, and biliary secretions; (2) decreased absorption of water and sodium from the intestinal lumen; and (3) increased secretion of water and sodium into the lumen of the distended segment. Shields[5] described an *in vivo* model of ileal obstruction in dogs. He found decreased absorption of water and sodium in the obstructed segments followed by increased secretion of water and sodium intraluminally as distension increased. These findings were confirmed by Wright et al.[6] who produced temporary ileal obstruction with balloons in humans with ileostomies. A vicious cycle of decreased absorption and increased secretion occurs in distended, obstructed ileal segments.

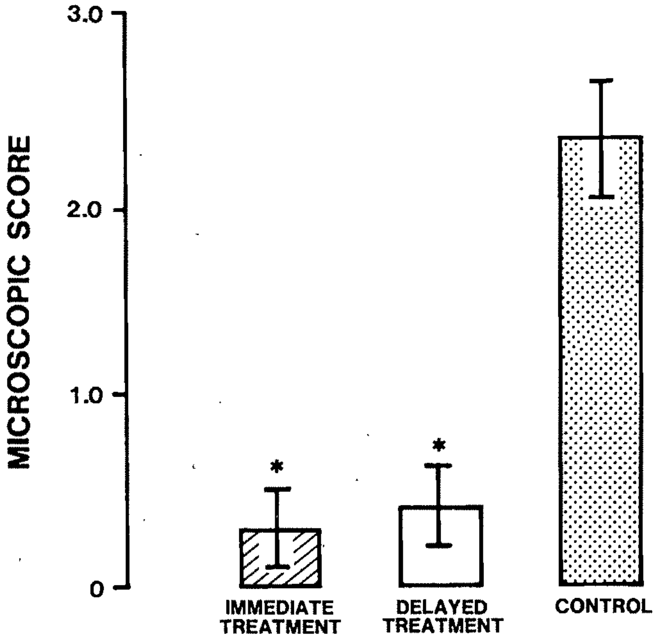

FIG. 4. Microscopic pathologic score from ileum with closed-loop obstruction with and without SS-14 treatment. $*p < 0.05$ compared to control.

SS-14 has been shown *in vitro* to increase water and electrolyte absorption in rabbit ileum[7,8] and to inhibit water secretion in rat jejunum.[9] Additionally, numerous studies have demonstrated inhibition of gastric, biliary, and pancreatic secretion by SS-14.[3,10] These studies, as well as several clinical reports of control of secretory diarrhea by SS-14,[11,12] led us to test the efficacy of SS-14 in the management of the intestinal secretory disturbances caused by mechanical small bowel obstruction.

In our study, uniform closed-loop obstructed ileal segments were created, resulting additionally in proximal simple obstructions in anesthetized rabbits. All rabbits were maintained with intravenous hydration, and all survived the 24-hour study period. Intestinal obstruction in these rabbits led to marked distension, cyanosis, and patchy necrosis, particularly in the closed-loop segments. These findings were prevented by SS-14 treatment, even when onset of treatment was delayed for 6 hours after obstruction. In addition to the marked decreases in intestinal luminal volume seen in treated rabbits, significant reductions in sodium and potassium output were present, implying inhibition of water, sodium, and potassium secretion in the obstructed intestine by SS-14. Alternatively, the effects noted could have been due to enhanced absorption by SS-14 of water and

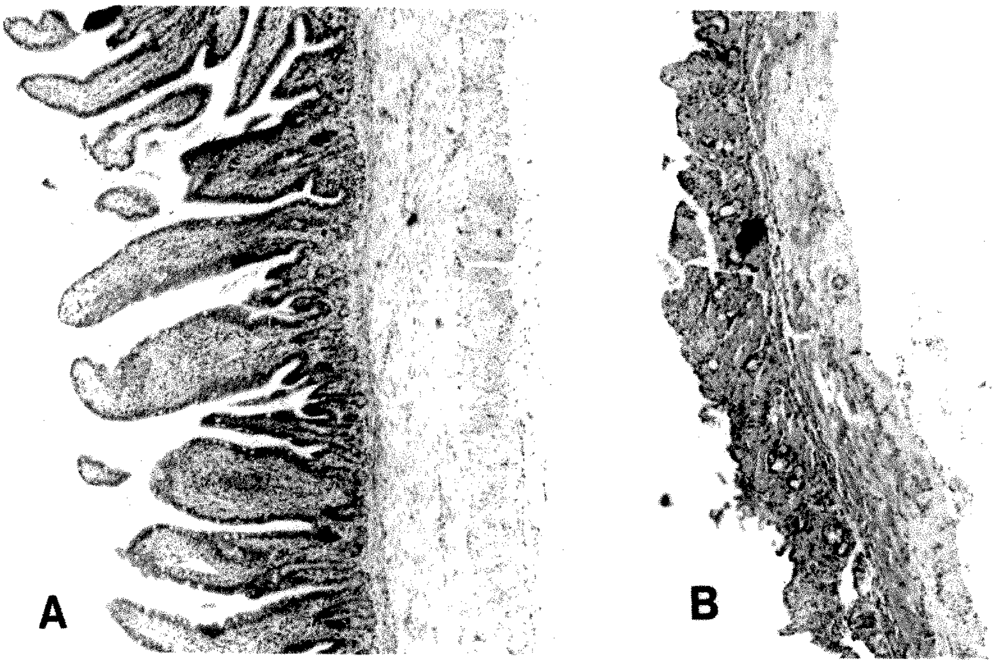

FIG. 5. Representative microscopic sections stained with hematoxylin and eosin from rabbit ileum with closed-loop obstruction (original magnification ×40). *A*. SS-14 treatment. *B*. Control.

electrolytes from the obstructed bowel. The present study was not designed to examine in detail the mechanisms involved in the protection afforded by somatostatin. It is possible mechanisms other than prevention of distension by luminal fluid also operate when somatostatin is employed. For example, with ischemia powerful vasoactive substances [*e.g.*, vasoactive intestinal peptide (VIP)] are released locally in the gut wall.[13] Somatostatin may inhibit release of such agents and protect microcirculation failure and edema and hemorrhage in the bowel wall. Future studies will be designed to examine the protective mechanisms of somatostatin in small bowel obstruction.

It is clear that SS-14 treatment cannot correct the underlying pathology when complete mechanical small bowel obstruction exists. However, the ability to prevent further distension by pharmacologic inhibition of gastrointestinal, biliary, and pancreatic secretion may be of value as an adjunct to I.V. fluid repletion and diagnostic studies in patients with complete small bowel obstruction. Additionally, and perhaps more importantly, such pharmacologic manipulation may aid management of patients with partial small bowel obstruction, the vast majority of whom do not require operative treatment. Additionally, patients with obstruction related to malignancy and obstruction in the early postoperative period, both settings where nonoperative management is preferable, may benefit from pharmacologic reduction of intestinal luminal volume. We believe additional animal studies and subsequent controlled clinical trials are necessary before somatostatin can be used as a clinical adjunct in the treatment of small bowel obstruction.

Acknowledgment

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Colonoscopic Detection of Early Colorectal Cancers

Impact of a Surgical Endoscopy Service

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The Surgical Endoscopy Service has been aggressively evaluating gastrointestinal symptoms with colonoscopy and screening asymptomatic patients with flexible sigmoidoscopy in hopes of finding early curable colorectal cancers. The purpose of this study was to compare the stages of colorectal cancers resected during the 18-month period prior to (Pre-SES) and during the first 18 months (Post-SES) after the creation of the Surgical Endoscopy Service. In addition, the yield of lesions that would have been obtained by depending upon patient symptoms or occult blood testing were determined. A total of 361 colonoscopies were performed Pre-SES and 874 colonoscopies Post-SES; 26 patients underwent resection of colorectal cancers Pre-SES and 32 Post-SES. Whereas early colorectal cancers (Dukes' A and B_1) were found in only three patients (12%) Pre-SES period, early cancers were found in 13 (41%) Post-SES. Doubling the number of colonoscopies produced a fourfold increase in the number of early lesions. Furthermore, disseminated cancers (D lesions) dropped from 19% Pre-SES to 3% Post-SES. Among the total 58 patients, 43% of the A lesions and 40% of the B_1 lesions were asymptomatic. Even more alarming, 86% of the A lesions, 50% of the B_1 lesions, 31% of the B_2 lesions, and 14% of the C_2 lesions were occult blood negative. Indeed, only the D lesions were uniformly occult blood positive. This study demonstrates that aggressive colonoscopy detects early colorectal cancers. Moreover, patient symptoms or occult blood testing will fail to indicate the majority of early colorectal cancers.

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THERE ARE MORE THAN 130,000 new cases of colorectal cancer each year in the United States.[1] Despite this rising incidence, few advances in the treatment of colorectal cancer have been achieved. Indeed, survival of patients with colorectal cancers has not significantly changed in the last three decades.[2] Furthermore, adjuvant chemotherapy, radiotherapy, or immunotherapy have not altered at all treatment results of patients with colorectal cancers.[3] Little hope exists, therefore, of improving therapeutic results in patients with colorectal cancer. Consequently, an alternative strategy must be pursued if the death rate from colorectal cancer is to be diminished.

Results of treating early colorectal cancer are excellent. Sir Edward Hughes reported an 80% survival rate in treating patients with Dukes' A lesions (*i.e.*, lesions limited to the bowel wall without lymph node involvement).[4] Turnbull reported a 98% 5-year survival rate for 103 patients with Dukes' A lesions.[5] These results would suggest that the best hope of improving survival rates of patients with colorectal cancer lies in finding these cancers while they remain confined to the bowel wall rather than striving for new modalities for treating advanced or disseminated disease.

Much effort has been invested in evaluating various methods for screening large populations for colorectal cancer. Testing stool for occult blood has been an attractive technique for performing screening tests for several reasons; the tests are inexpensive, easy to perform, and the results are easy to interpret. Unfortunately, no study that has tested a population for occult blood in stool has succeeded in decreasing colon cancer-related deaths in that population.[6-10]

Proctosigmoidoscopy is an effective means of detecting rectal cancers.[11] In a large prospective study at the University of Minnesota, Gilbertson succeeded in nearly obviating the occurrence of rectal cancer in a population of patients that he routinely screened with a rigid proctosigmoidoscope.[12] Unfortunately, the percentage of colorectal cancers now within the reach of the rigid scope is rapidly dropping. Greene found only 26% of colorectal cancers in the rectum and only another

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28% throughout the sigmoid colon.[13] It would seem from these studies that endoscopic evaluation of the colon and rectum is the best means of identifying colorectal cancers and that flexible endoscopic instruments are necessary for reaching the majority of these lesion.

The purpose of this study was to determine the effect of the surgical endoscopy service on the stage of colorectal cancer surgically treated in our institution. Specifically, we established the number of colonoscopies performed in the West Haven Veterans Administration Hospital during the 18 months prior to the onset of the surgical endoscopy service and during the subsequent 18 months. In addition, we compared the stage of each colorectal cancer treated during these two time periods. Furthermore, we contrasted the yield of early colorectal cancers obtained by endoscopic evaluation of the colon with that obtained from a careful history and that from testing the stool for occult blood. The results of this study suggest that aggressive colonoscopy is the best means for uncovering early curable colorectal cancers.

Materials and Methods

We retrospectively reviewed the charts of all patients surgically treated for colorectal cancers at the West Haven Veterans Administration Medical Center during a 36-month period. One group of patients was identified during the 18-month time frame from April 1, 1983 to September 30, 1984. This was deemed the Pre-Surgical Endoscopy Service (Pre-SES) time period. The second group of patients was treated during the first 18-month period after the onset of the surgical endoscopy service: October 1, 1984 to March 31, 1986. This was deemed the Post-Surgical Endoscopy Service (Post-SES) time period.

Data was extracted from the hospital charts of the patients. The patients' age, sex, chief complaint, indication for evaluation, and stool occult blood status were culled from the chart. Occult blood tests were performed on fresh stool specimens obtained by physicians during physical examinations. No patient was placed on special diets before stool occult blood testing, and samples were not rehydrated before testing. For most patients, more than one stool occult blood test was available. The patient was judged occult blood positive if any one stool occult blood test was positive or trace positive. Endoscopy reports and operative notes were reviewed to determine the position of the lesion and the extent of disease. Pathology reports were reviewed to determine the depth of bowel wall penetration of the lesion and for the presence of lymph node metastases. If the pathology report was ambiguous about the depth of penetration, the original pathology slides were reviewed. Based on this information, each lesion was staged by the Astler-Coller modification[14] of the Dukes'[15] classification for carcinoma of the colon and rectum (Table 1). In addition, a D stage was included as suggested by Turnbull.[16] All data were entered into a computerized data base system (Symphony, Lotus Development Corporation, Cambridge, MA) for analysis. Results were tabulated for each time period, Pre-SES and Post-SES. In addition, the data were compiled for the entire 36-month time period. Results were expressed as mean and SEM. When groups were compared, significance was judged as $p < 0.05$) using Student's t-test for unpaired samples.

TABLE 1. *Modified Dukes' Classification of Astler and Coller with Addition of a D Category*[14-16]

Stage	Definition
A	Limited to mucosa
B_1	Invasion of muscularis mucosa, submucosa, or musularis propria
B_2	Complete penetration of muscularis propria
C_1	Invasion of muscularis mucosa; lymph nodes involved
C_2	Complete penetration of muscularis propria; lymph node involved
D	Distant metastases

Results

There were 58 patients found to be eligible for the study, 26 in the Pre-SES period, and 32 patients during the Post-SES period. The age of the patients in both groups was similar; the average in the Pre-SES group A was 66.2 years ± 2.2 and in the Post-SES group 66.6 years ± 2.0. All patients in both groups were men.

The chief complaints for these 56 patients are listed in Table 2. Only 7.7% of Pre-SES patients were without symptoms when their colorectal carcinoma was discovered. In contrast, 28.1% of Post-SES patients were asymptomatic. The distribution of other chief complaints was otherwise similar between the two groups.

The duration of symptoms prior to seeking medical attention is listed in Table 3 for both groups. The aver-

TABLE 2. *The Chief Complaints for 56 Patients who Underwent Surgical Treatment at the West Haven VA Medical Center*

Chief Complaint	Pre-SES (N = 26)		Post-SES (N = 32)	
	Number	%	Number	%
None	2	7.7	9	28.1
Pain	10	38.5	9	28.1
Bleeding	3	11.5	5	15.6
Constipation	4	15.4	3	9.5
Distension	2	7.7	1	3.1
Weight loss	2	7.7	4	12.5
Diarrhea	3	11.5	1	3.1
Total	26	100	32	100

TABLE 3. *Duration of Symptoms Prior to Seeking Medical Attention in 56 Patients Surgically Treated at the West Haven VA Medical Center*

Duration of Symptoms (mo)	Pre-SES (N = 26)		Post-SES (N = 32)	
	Number	%	Number	%
0	3	11.5	9	28.1
1	1	3.8	2	6.2
2	8	30.9	10	31.3
3	3	11.5	3	9.4
4	2	7.7	2	6.2
5	0	0	0	0
6	6	23.1	3	9.4
8	1	3.8	0	0
12	2	7.7	3	9.4
Total	26	100	32	100

age duration of symptoms for Pre-SES patients (3.9 ± 0.6 months) and for Post-SES patients (2.9 ± 0.6 months) were not significantly different ($p > 0.05$).

Pre-SES patients had a greater percentage of left-sided lesions than Post-SES patients (Table 4). In the Pre-SES group, 9 of 26 (34.6%) lesions were in the cecum, ascending colon, hepatic flexure, or transverse colon. In the Post-SES group, 14 of 32 (43.8%) lesions were in these locations. The greater number of cecal lesions in Post-SES group accounts for this greater proportion of right-sided lesions.

TABLE 4. *Location of 56 Adenocarcinomas Treated at the West Haven VA Medical Center*

Location	Pre-SES (N = 26)		Post-SES (N = 32)	
	Number	%	Number	%
Cecum	2	7.8	6	18.8
Ascending colon	5	19.2	6	18.8
Hepatic flexure	1	3.8	0	0
Transverse colon	1	3.8	2	6.2
Splenic flexure	1	3.8	2	6.2
Descending colon	3	11.5	3	9.4
Sigmoid colon	7	27.0	3	9.4
Rectum	6	23.1	9	28.1
Multiple cancers	0	0	1	3.1
Total	26	100	32	100

TABLE 5. *Distribution by Stage of 56 Patients Treated for Colorectal Cancers at the West Haven VA Medical Center*

Stage	Pre-SES (N = 26)		Post-SES (N = 32)	
	Number	%	Number	%
Dukes' A	1	3.8	6	18.8
Dukes' B_1	2	7.7	8	25.0
Subtotal	3	11.5	14	43.8
Dukes' B_2	8	30.9	5	15.7
Dukes' C_1	1	3.8	6	18.7
Dukes' C_2	9	34.6	6	18.7
Dukes' D	5	19.2	1	3.1
Subtotal	23	88.5	18	56.2
Total	26	100	32	100

Patients Pre-SES tended to have more advanced lesions at the time of treatment (Table 5). Among Pre-SES patients, only three patients had early lesions (11.5%); one patient (3.8%) had a Dukes' A lesion, and two patients (7.7%) a Dukes' B_1 lesion. In sharp contrast, 14 Post-SES patients (43.8%) had early lesions; 6 with Dukes' A lesions (18.8%), and 8 with Dukes' B_1 lesions (25.0%). This represents a nearly fourfold increase in the number of early colorectal cancers. In addition, there was a marked decline in the number of Dukes' D lesions in Post-SES patients as compared to Pre-SES patients—5 of 26 (19.2%) lesions Pre-SES *versus* 1 of 32 lesions (3.1%) Post-SES.

The number of patients who were asymptomatic at the time that their colorectal cancer was diagnosed is listed in Table 6. Whereas symptoms were absent in more than 40% of patients with A or B_1 lesions, symptoms were present in more than 90% of patients with advanced lesions. Overall, only 19% of patients were asymptomatic at the time of diagnosis.

Occult blood testing poorly detected early colorectal cancers. Although overall 16 of 58 patients (73%) were occult blood positive, 11 of 17 patients (65%) with early colorectal cancers were occult blood negative. Figure 1 demonstrates the per cent of patients that were occult blood negative for each stage of cancer. Of particular importance is the fact that 86% of patients with Dukes' A lesions and 50% of patients with Dukes' B_1 lesions were occult blood negative.

Discussion

In this study we have compared the number of colonoscopies performed and the stages of colorectal cancer treated in our hospital during two consecutive time periods: Pre-SES and Post-SES. The number of colonoscopies more than doubled from the first time period to the second. A dramatic shift in stage of colorectal cancers was also demonstrated from the first period to the second. In fact, doubling the number of colonoscopies from the first period to the second resulted in uncovering a fourfold increase in the number of early colorectal cancers (Dukes' A and B_1 lesions). This study demonstrates the ability of aggressive colonoscopy to increase the detection rate of early colorectal cancers.

This study has also demonstrated that traditional means of detecting colorectal cancers fail to detect early lesions. Among the 58 patients treated during the 36-month study period, 43% of patients with A lesions and

40% of patients with B_1 lesions complained of no symptoms. Thus, history alone would have missed 41% of early (Dukes' A and B_1 lesions) colorectal cancers. Once a patient develops symptoms from his colorectal malignancy, the lesion is generally advanced or, indeed, disseminated.

Additionally, this study has demonstrated that occult blood testing fails to detect early colorectal cancer. Among these patients, 86% of A lesions and 50% of B_1 lesions were occult blood negative. Consequently, 65% of early colorectal cancers in our patients were not detected by the occult blood test. These data indicate that under most circumstances, only advanced or disseminated colorectal cancers produce symptoms or loose blood into the stool.

In our study, the occult blood test was falsely negative in 27.6% of all patients with colorectal cancers. This is consistent with other studies. Wexner et al.[17] reported that the occult blood test was negative in 44% of 100 patients with colorectal cancers. Crowley et al.[18] reported the occult blood test was positive in only 52% of 213 patients with colorectal cancers. Recent reviews estimated the false-negative rate for occult blood testing in patients with colorectal cancers as between 40% and 60%.[9,19,20]

Occult blood testing poorly detects right-sided carcinomas. In the Nottingham study only one carcinoma was detected beyond the splenic flexure in 3613 patients who underwent fecal blood testing.[21] In the University of Minnesota study, 38 carcinomas were detected beyond the splenic flexure in 48,000 patients.[22] At the Hines VA, four carcinomas were detected beyond the splenic flexure in 2964 patients.[23] In Erie County, New York, two proximal colon carcinomas were detected among 3822 patients.[7] In these four studies then, 8.3% of the Nottingham carcinomas, 33.6% of the Minnesota carcinomas, and 28.5% of the Hines carcinomas and 28.6% of the Erie County carcinomas were beyond the splenic flexure. This low yield of carcinomas from beyond the splenic flexure is consistent with the yield of proximal carcinomas in our Pre-SES period (34.6%). The higher percent of proximal carcinomas in our Post-SES period (43.8%) and the results of other studies,[13] however, suggest that occult blood testing failed to detect a substantial number of proximal colorectal cancers.

The best means of performing the occult blood test remains ill defined. In our study, patients were not given any dietary restrictions, the stool smear was not rehydrated before development, and no specific number of occult blood tests were performed though several were generally obtained. If any one test was positive, the patient was counted as being occult blood positive. Some consider special diets for 3 days prior to testing as an integral part of occult blood testing.[7] Many components of a normal diet may cause a falsely positive occult blood test. Several of these include radishes, broccoli, cantaloupe, turnips, bean sprouts, cauliflower, red meats, and iron.[19] Others state that dietary restrictions only decrease the specificity of the test.[24] Similarly, no uniformity of opinion exists as to the best number of stool samples that should be tested. Greegor[25] initially suggested testing six stool smears from three different bowel movements. Macrae has pointed out that increasing the number of tests increases the sensitivity of occult blood testing but diminishes the specificity.[24] Other techniques that serve to increase the sensitivity of occult blood testing, such as rehydrating the smeared stool sample before applying the developing solution, also decrease the specificity.[10] Unfortunately, it remains true that no prospective trial has compared these variables in a controlled fashion and, thus, the best means of administering the stool occult blood test remains uncertain.

TABLE 6. *The Number of Patients with Occult Blood Absent (−) in Their Stools and the % Without Symptoms are Listed for 58 Patients Treated at the West Haven VA Medical Center During the 36-Month Study Period*

	Occult Blood −		Asymptomatic	
Stage	Number	%	Number	%
Dukes' A	6/7	85.7	3/7	42.9
Dukes' B_1	5/10	50.0	4/10	40.0
Subtotal	11/17	64.7	7/17	41.2
Dukes' B_2	4/13	30.8	2/13	15.4
Dukes' C_1	1/7	14.3	1/7	14.3
Dukes' C_2	0/15	0	0/15	0
Dukes' D	0/6	0	1/6	16.7
Subtotal	5/41	12.2	4/41	9.8
Total	16/58	27.6	11/58	19.0

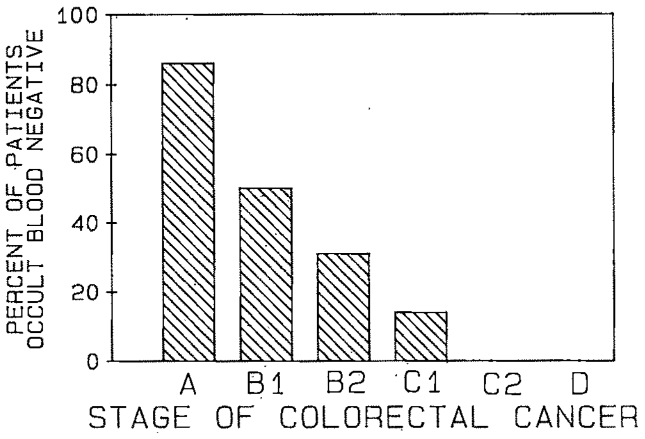

FIG. 1. Per cent of patients with occult blood negative stools grouped by stage of colorectal cancer. These results indicate that testing stool for occult blood detects few early colorectal cancers.

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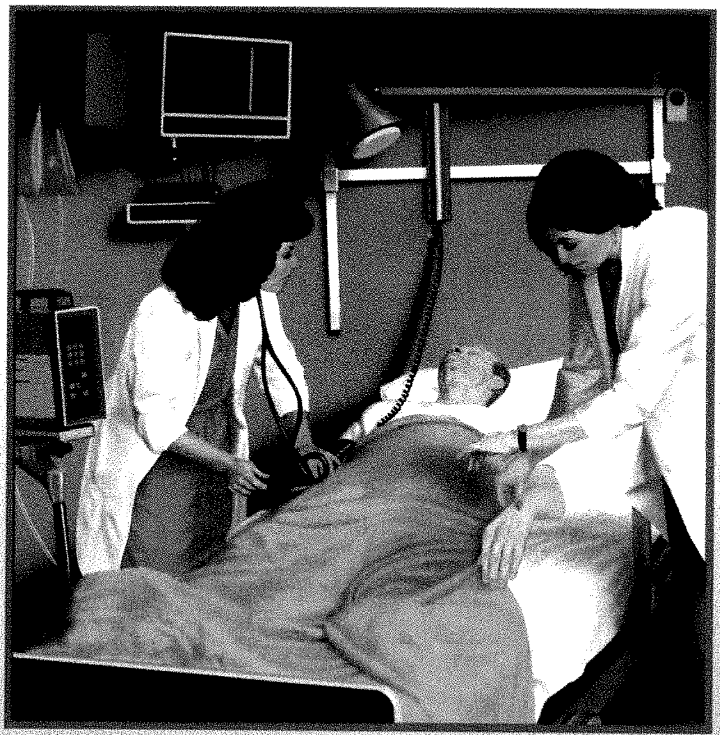
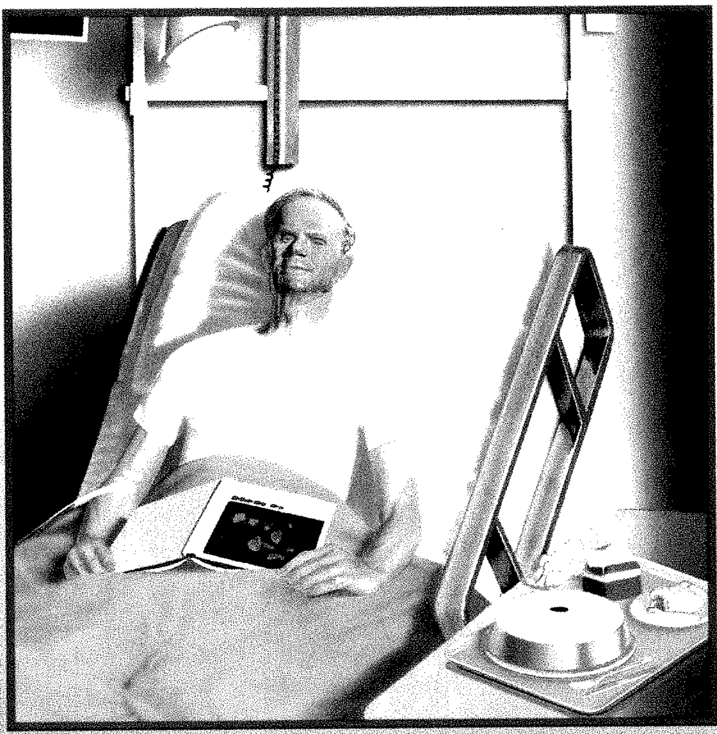
INFECTION IN THE ELDERLY PATIENT



"NEPHROTOXICITY LIMITS THE CLINICAL UTILITY OF AMINOGLYCOSIDES."[1]

AZACTAM®
AZTREONAM



IN ELDERLY PATIENTS—GRAM-NEGATIVE EFFICACY WITHOUT AMINOGLYCOSIDE TOXICITY

AZACTAM®
AZTREONAM
FOR INJECTION

CLINICAL EFFICACY PROVEN IN STUDIES WITH NEARLY 300 ELDERLY PATIENTS[2-9]

- Efficacy comparable to aminoglycosides, with excellent activity against a wide range of susceptible gram-negative aerobic organisms, including *Pseudomonas aeruginosa*[2-4]

SUPERIOR SAFETY PROFILE[*2,3,10]—
ESPECIALLY IMPORTANT IN ELDERLY PATIENTS

- Does not cause nephrotoxicity[†10-13]
- Does not cause ototoxicity[10,11]
- Requires no costly routine blood monitoring[‡]
- Avoids the costs that nephrotoxicity adds to all patients on aminoglycoside therapy (average $183/patient)[14]

[*] Dosage adjustment, based on estimated creatinine clearance, may be necessary in elderly patients.

For a discussion of INDICATIONS AND USAGE (including susceptible organisms), CONTRAINDICATIONS, PRECAUTIONS, and ADVERSE REACTIONS, please consult brief summary on adjacent page.

[†] Demonstrated in animal studies, and in human volunteer studies involving 36 subjects. In clinical trials involving 4,570 subjects, transient elevations in serum creatinine were rarely observed.

[‡] Renal function should be monitored when AZACTAM (aztreonam) is used concomitantly with aminoglycosides. In patients with impaired hepatic or renal function, appropriate monitoring is recommended during therapy.

INSTEAD OF AMINOGLYCOSIDES...
ESPECIALLY IN ELDERLY PATIENTS

ACT AZACTAM®
AZTREONAM

AZACTAM® FOR INJECTION

Aztreonam For Injection

DESCRIPTION—AZACTAM (aztreonam, Squibb) is the first member of a new class of antibiotics classified as monobactams. AZACTAM is a totally synthetic bactericidal antibiotic with activity against a wide spectrum of gram-negative aerobic pathogens. The monobactams, having a unique monocyclic beta-lactam nucleus, are structurally different from other beta-lactam antibiotics.

AZACTAM For Injection is a sterile nonpyrogenic white powder, containing approximately 780 mg L-arginine per gram of aztreonam, for intramuscular or intravenous use following constitution. The powder is sodium-free. Aqueous solutions of aztreonam have a pH in the range of 4.5 to 7.5.

INDICATIONS AND USAGE—Before initiating treatment with AZACTAM, appropriate specimens should be obtained for isolation of the causative organism(s) and for determination of susceptibility to aztreonam. Treatment with AZACTAM may be started empirically before results of the susceptibility testing are available; subsequently, appropriate antibiotic therapy should be continued.

AZACTAM For Injection is indicated for the treatment of the following infections caused by susceptible gram-negative microorganisms: **Urinary Tract Infections** (complicated and uncomplicated), including pyelonephritis and cystitis (initial and recurrent) caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Enterobacter cloacae, Klebsiella oxytoca**, *Citrobacter* species* and *Serratia marcescens**. **Lower Respiratory Tract Infections,** including pneumonia and bronchitis caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Haemophilus influenzae, Proteus mirabilis, Enterobacter* species and *Serratia marcescens**. **Septicemia** caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis**, *Serratia marcescens** and *Enterobacter* species. **Skin and Skin-Structure Infections,** including those associated with postoperative wounds, ulcers and burns caused by *Escherichia coli, Proteus mirabilis, Serratia marcescens, Enterobacter* species, *Pseudomonas aeruginosa, Klebsiella pneumoniae,* and *Citrobacter* species*. **Intra-abdominal Infections,** including peritonitis caused by *Escherichia coli, Klebsiella* species, including *K. pneumoniae, Enterobacter* species including *E. cloacae**, *Pseudomonas aeruginosa, Citrobacter* species* including *C. freundii** and *Serratia* species* including *S. marcescens**. **Gynecologic Infections,** including endometritis and pelvic cellulitis caused by *Escherichia coli, Klebsiella pneumoniae**, *Enterobacter* species* including *E. cloacae**, and *Proteus mirabilis**.

AZACTAM is indicated for adjunctive therapy to surgery in the management of infections caused by susceptible organisms, including abscesses, infections complicating hollow viscus perforations, cutaneous infections and infections of serous surfaces. AZACTAM is effective against most of the commonly encountered gram-negative aerobic pathogens seen in general surgery.

Concurrent Therapy—Concurrent initial therapy with other antimicrobial agents and AZACTAM is recommended before the causative organism(s) is known in seriously ill patients who are also at risk of having an infection due to gram-positive aerobic pathogens. If anaerobic organisms are also suspected, therapy should be initiated using an antianaerobic agent concurrently with AZACTAM. Certain antibiotics (e.g., cefoxitin, imipenem) may induce high levels of beta-lactamase *in vitro* in some gram-negative aerobes such as *Enterobacter* and *Pseudomonas* species, resulting in antagonism to many beta-lactam antibiotics including aztreonam. These *in vitro* findings suggest that such beta-lactamase inducing antibiotics not be used concurrently with aztreonam. Following identification and susceptibility testing, appropriate antibiotic therapy should be continued.

CONTRAINDICATIONS—Aztreonam is contraindicated in patients with known allergy to this antibiotic.

WARNINGS—Careful inquiry should be made for a history of hypersensitivity reaction to any antibiotic or other drugs. Antibiotics should be given with caution to any patient who has had some form of allergy, particularly to drugs. It is recommended that patients who have had immediate hypersensitivity reactions (e.g., anaphylactic or urticarial) to penicillins and/or cephalosporins should be followed with special care. If an allergic reaction to aztreonam occurs, discontinue the drug and institute supportive treatment as appropriate (e.g., maintenance of ventilation, pressor amines, antihistamines, corticosteroids). Serious hypersensitivity reactions may require epinephrine and other emergency measures.

PRECAUTIONS—General: In patients with impaired hepatic or renal function, appropriate monitoring is recommended during therapy. If an aminoglycoside is used concurrently with aztreonam, especially if high dosages of the former are used or if therapy is prolonged, renal function should be monitored because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. The use of antibiotics may promote the overgrowth of nonsusceptible organisms, including gram-positive organisms and fungi. Should superinfection occur during therapy, appropriate measures should be taken.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Carcinogenicity studies in animals have not been performed. Genetic toxicology studies performed *in vivo* and *in vitro* with aztreonam in several standard laboratory models revealed no evidence of mutagenic potential at the chromosomal or gene level. Two-generation reproduction studies in rats at daily doses up to 20 times the maximum recommended human dose, prior to and during gestation and lactation, revealed no evidence of impaired fertility. There was a slightly reduced survival rate during the lactation period in the offspring of rats that received the highest dosage, but not in offspring of rats that received five times the maximum recommended human dose.

Pregnancy—Pregnancy Category B: Aztreonam crosses the placenta and enters the fetal circulation. Studies in pregnant rats and rabbits, with daily doses up to 15 and 5 times, respectively, the maximum recommended human dose, revealed no evidence of embryo- or fetotoxicity or teratogenicity. No drug induced changes were seen in any of the maternal, fetal or neonatal parameters that were monitored in rats receiving 15 times the maximum recommended human dose of aztreonam during late gestation and lactation. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, aztreonam should be used during pregnancy only if clearly needed.

Nursing Mothers—Aztreonam is excreted in breast milk in concentrations that are less than 1% of concentrations determined in simultaneously obtained maternal serum; consideration should be given to temporary discontinuation of nursing and use of formula feedings.

Pediatric Use—Safety and effectiveness have not been established in infants and children.

ADVERSE REACTIONS—Local reactions such as phlebitis/thrombophlebitis following IV administration, and discomfort/swelling at the injection site following IM administration occurred at rates of approximately 1.9% and 2.4%, respectively. Systemic reactions (considered to be related to therapy or of uncertain etiology) occurring at an incidence of 1 to 1.3% include diarrhea, nausea and/or vomiting, and rash. Reactions occurring at an incidence of less than 1% are listed within each body system in order of decreasing severity: *Hypersensitivity*—anaphylaxis. *Hematologic*—pancytopenia, neutropenia, thrombocytopenia, anemia, leukocytosis, thrombocytosis. *Gastrointestinal*—abdominal cramps; rare cases of *C. difficile*-associated diarrhea or gastrointestinal bleeding have been reported. *Dermatologic*—purpura, erythema multiforme, urticaria, exfoliative dermatitis, petechiae, pruritus, diaphoresis. *Cardiovascular*—hypotension, transient ECG changes (ventricular bigeminy and PVC). *Respiratory*—one patient experienced flushing, chest pain, and dyspnea. *Hepatobiliary*—hepatitis, jaundice. *Nervous System*—seizure, confusion, vertigo, paresthesia, insomnia, dizziness. *Musculoskeletal*—muscular aches. *Special Senses*—tinnitus, diplopia, mouth ulcer, altered taste, numb tongue, sneezing and nasal congestion, halitosis. *Other*—vaginal candidiasis, vaginitis, breast tenderness. *Body as a Whole*—weakness, headache, fever, malaise.

Adverse Laboratory Changes—Those reported without regard to drug relationship during clinical trials were: *Hepatic*—elevations of AST (SGOT), ALT (SGPT), and alkaline phosphatase; signs or symptoms of hepatobiliary dysfunction occurred in less than 1% of recipients (see above). *Hemic*—increases in prothrombin and partial thromboplastin times, eosinophilia, positive Coombs test. *Renal*—increases in serum creatinine.

OVERDOSAGE—If necessary, aztreonam may be cleared from the serum by hemodialysis and/or peritoneal dialysis.

DOSAGE AND ADMINISTRATION—Dosage adjustments are recommended for patients with impaired renal function. In elderly patients, estimates of creatinine clearance should be obtained and appropriate dosage modifications made if necessary.

HOW SUPPLIED—AZACTAM For Injection (Aztreonam For Injection) is supplied in single-dose 15 mL vials containing **500 mg, 1 g** or **2 g** per vial, and in single-dose 100 mL intravenous infusion bottles containing **500 mg, 1 g** or **2 g** per bottle.

Consult package insert before prescribing AZACTAM (aztreonam).

(J4-140)

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*Efficacy for this organism in this organ system was studied in fewer than ten infections.

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Epidural Spinal Cord Electrical Stimulation Improves Microvascular Blood Flow in Severe Limb Ischemia

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Epidural spinal cord electrical stimulation (ESES) was performed on 10 patients with severe limb ischemia due to atherosclerotic disease. Microcirculatory parameters were assessed before and after ESES. Bright field microscopy was used to assess capillary diameters and red blood cell (RBC) velocity in the dorsum of the foot. Fluorescein microscopy was used with intravenously injected sodium fluorescein to study capillary density and sodium fluorescein appearance time in the dorsum of the toe. The systolic ankle/arm pressure ratio and toe pressure measurements were used as macrocirculatory parameters. After ESES, clinical improvement was confirmed by intravital microscopy. Capillary density increased ($p < 0.001$), RBC velocity in capillaries already perfused before ESES increased from 0.054 mm/sec to 0.762 mm/sec ($p < 0.001$), and sodium fluorescein appearance time decreased from 72 to 45 seconds ($p < 0.001$). Capillary diameter did not change significantly so that the increase in RBC velocity may be interpreted as enhanced volume flow. Systolic ankle/arm pressure ratios and digital arterial pressure did not change significantly. The current results show that in patients with severe occlusive arterial disease of the lower limbs, ESES recruits capillaries not perfused in the control situation and enhances skin blood flow, improvements that may explain the beneficial clinical effects of ESES.

THE SYMPTOMS OF atherosclerotic occlusive arterial disease of the lower limb include intermittent claudication at a relatively early stage of the disease, followed by ischemic rest pain, ulceration, and gangrene as the disease progresses. Vascular surgery is the therapy of choice, but in approximately 20% of the patients with stage IV disease, according to Fontaine, reconstructive surgery is not effective anymore.[1] In these patients, lumbar sympathectomy[2] and conservative treatment[3] generally fail to improve blood supply to the limb and amputation is the last alternative treatment.[3]

Epidural spinal electrical stimulation (ESES) is a medically accepted therapeutic modality for the control of chronic pain. The best results with ESES have been obtained in patients with intractable low back pain, causalgia, and phantom limb pain.[4] Recently, spinal cord stimulation was also successfully used in patients with ischemic rest pain. Strikingly enough, not only pain relief was achieved, but also healing of ischemic ulcers occurred,[5] suggesting that ESES improves nutritional blood flow. Attempts have been made to delineate these beneficial, clinical effects with the use of the xenon washout technique,[6] ankle pressure measurements,[7,8] or photoplethysmography.[9,10] These macrocirculatory techniques, however, are not sensitive enough to evaluate the effect of ESES on the microcirculatory disturbances, occurring in patients with ulcers and gangrene. In these patients, evaluation of treatment should ideally take place at the level at which the ischemic phenomena occur: the skin nutritional capillaries. Intravital capillary microscopy is a noninvasive method to study the morphologic pattern of the microcirculation[11] and allows the measurement of red blood cell velocity in the skin capillaries, which specifically reflects nutritional blood flow.[12] This technique enables objective evaluation of treatment and can even discriminate respondents from nonrespondents to treatment.[13]

The aim of this study was to evaluate the effects of ESES on microcirculatory blood flow. Morphologic and dynamic capillary microscopy was performed before and after ESES in 10 patients with severe lower limb ischemia.

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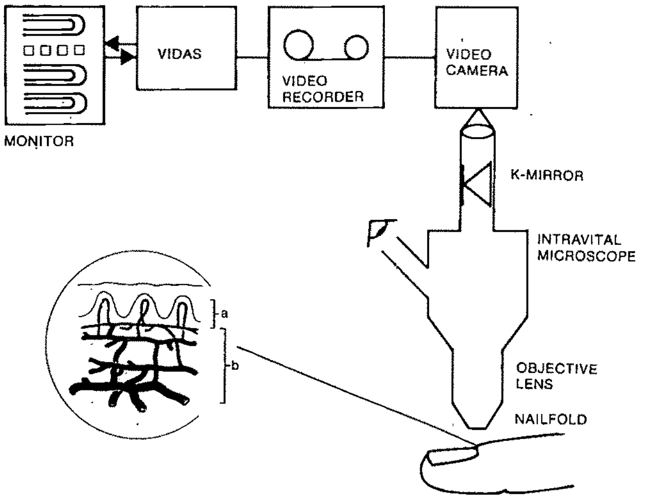


FIG. 1. Schematic representation of the set up for capillaroscopy and of the skin vascular bed, showing the nutritional (a) and thermoregulatory (b) part of skin blood supply.

Patients and Methods

Patients

ESES was performed on 10 patients with occlusive arterial disease of the lower limbs due to atherosclerosis, combined with diabetes in four patients. The mean age of these eight men and two women was 77 years (range: 72–84 years).

Before ESES, patients had vascular reconstructive surgery or sympathectomy without satisfactory result. Angiography, either monoplanar translumbar aortography or biplane selective femoral punction arteriography, showed occluded crural arteries technically unsuitable for reconstructive surgery. Conservative treatment and vasodilating drugs were not effective. All patients had intolerable unilateral rest pain and eight of them had nonhealing ischemic ulcers. The only possible therapeutic alternative was limb amputation.

Protocol

The first patient was treated with ESES 15 months ago; the last patient was treated 2 months ago. Because of the short follow-up period, only the acute effects of ESES on vascular blood flow are presented. The following macro- and microcirculatory parameters were investigated 1 day before and 1 day after ESES.

Macrocirculation

The systolic ankle/arm pressure index, expressed as a percentage, was determined by dividing the systolic pressure, as measured over the posterior tibial or the dorsal pedal artery, by the systolic brachial artery pressure and multiplying this ratio by 100%. The pressure measurements were made with a bidirectional continuous wave Doppler instrument with a zero-crossing circuitry.

Photoplethysmography was used to measure the systolic pressure in the digital arterial system of the toe, using a pressure cuff around the proximal phalanx with a width of 1.5 cm. The systolic pressure was expressed in mmHg.

Microcirculation

Nutritional capillary blood flow and capillary morphology were studied by means of intravital microscopy with objectives L4× (numerical aperture NA = 0.04) and L10× (NA = 0.22). Figure 1 schematically represents the set up with a magnification of the skin microcirculation: arterioles and arteriovenous anastomoses, which form the thermoregulatory part of skin blood flow, and skin capillaries, which are responsible for the nutritional part of skin blood flow. The foot of the sitting patient was positioned on the stage of the microscope and fixed in a mass of clay. A drop of paraffin oil was applied to the nailfold and skin to minimize reflections. The technique of capillary microscopy has been described in detail before.[14,15] Essentially, the system (Fig. 1) consists of the microscope, which is connected with a television monitor through a low light level television camera. For offline analysis the images were stored on a videotape recorder. Capillaries were randomly chosen in the nailfold and dorsum of the skin of the foot to determine the following morphologic and dynamic parameters: (1) the density of the capillary loops, as measured with objective 4×. The density was expressed as the number of capillary loops per square millimeter. (2) The diameter of the capillary loop, using the objective 10×. Diameters were expressed in micrometers. (3) Capillary red blood cell (RBC) velocity, as measured with a video flying spot method.[16] In this technique, a spot moving over the videoscreen is synchronized with the moving red blood cells or plasma gaps. The advantage of this system is that very low RBC velocities can be measured accurately. (4) Appearance time of intravenously injected sodium fluorescein and number of capillaries perfused with this dye. Two milliliters of 10% sodium-fluorescein were injected intravenously, where on the arrival of the dye in the skin of the foot, was assessed with the use of a fluorescein microscope filter. The time between injection of the dye and arrival in the foot was defined as the appearance time, expressed in seconds. Furthermore, the number of capillaries filled with sodium-fluorescein was determined and expressed in number per square millimeter. Since sodium-fluorescein binds to plasma proteins, these capillaries filled with sodium-fluorescein do not only represent blood perfused capillaries, but also the capillaries perfused with plasma.

Surgical Procedure

Under local anesthesia, a vertical incision parallel to the spinal column was made. Through a Tuohy needle, an electrode was introduced into the epidural space at the level of L3–L4 and placed in the midline approximately at the level of T10. This was performed under x-ray control. The lead was manipulated until the patients experienced pleasant paresthesias extending down into both legs. Patients were stimulated either by external stimulation or by an internal device that was implanted in a subcutaneous pouch connected to the epidural electrode via a subcutaneous extension (Medtronic Inc., Minneapolis, MN).

Bipolar stimulation was performed with a pulse width of 0.2 msec and a frequency of 120 Hz. The amplitude varied between 4 and 9 V, depending on the patient's subjective feeling of comfortable paresthesias.

Statistical Analysis

In the tables, the data are presented as mean values and standard deviations. The Student's t-test was applied to evaluate the differences before and after ESES.

Results

Subjective Findings

Nine of the ten patients with severe rest pain showed immediate pain relief after spinal cord stimulation. In one patient pain was reduced, but displacement of the electrode caused unpleasant painful paresthesias. After a few weeks the electrode was removed. There was no difference in subjective findings between patients with and without diabetes. During the follow-up period, amputation was necessary in three patients, including the patient in whom ESES was stopped. These patients had gangrene before ESES. In the other five of the eight patients with ischemic ulcers, complete healing occurred in two patients and an improved tissue integrity was observed in three patients.

Objective Findings

Macrocirculation. Before ESES the mean systolic ankle/arm pressure index was 32%, which did not change after treatment (Table 1). The systolic toe pressure before treatment was 9 mmHg and increased to a mean value of 19 mmHg after ESES. This difference, however, was not statistically significant.

Microcirculation. Morphologic investigation of the skin capillaries revealed that both with and without sodium fluorescein the number of perfused capillaries increased significantly ($p < 0.001$) after ESES (Table 2). In Figure 2 the capillary bed filled with sodium-fluorescein is shown before and after stimulation. The obvious avascular areas before treatment are perfused after ESES. Skin capillary diameter (15.7 μm) did not change after treatment.

TABLE 1. *Macrocirculatory Parameters Before and After ESES**

	Before	After	Significance
Systolic ankle/arm pressure index (%)	32 ± 14	37 ± 14	NS
Systolic toe pressure (mmHg)	9 ± 16	19 ± 23	NS

* Mean ± SD.
NS = not significant.

Mean RBC velocity in the control situation was 0.054 mm/sec. One day after spinal cord stimulation, RBC velocity increased enormously in all patients to a mean value of 0.762 mm/sec ($p < 0.001$). The appearance time of sodium-fluorescein in the capillary bed significantly decreased in all patients ($p < 0.001$).

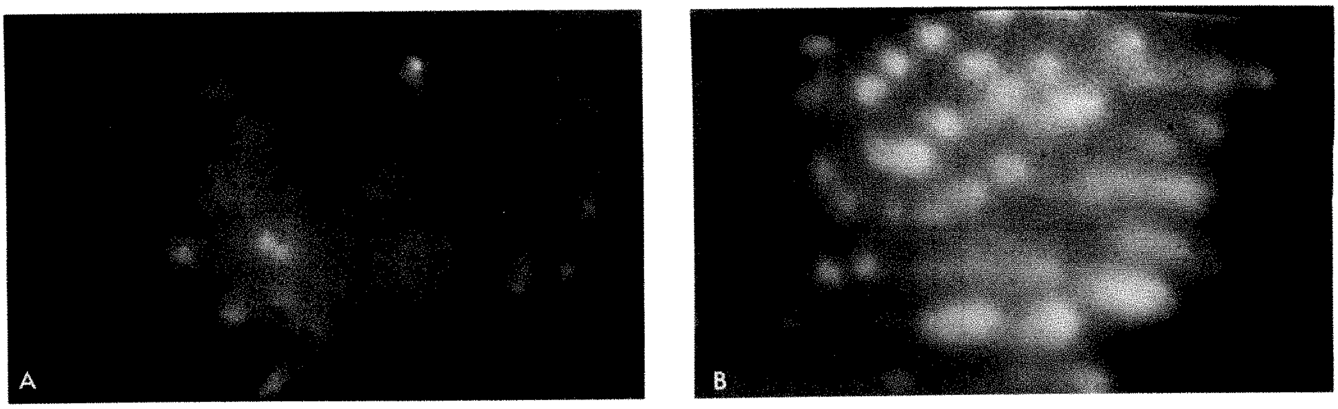
Discussion

In this study, skin capillary microscopy was shown to be a noninvasive method to evaluate microcirculatory changes induced by spinal cord stimulation. After ESES, the number of skin capillaries perfused and skin capillary RBC velocity significantly increased. The increase in velocity may be interpreted as an increase in skin blood flow rate because capillary diameter did not significantly change under these circumstances. The increase in skin capillary density and flow rate likely explain the observed clinical improvement and ulcer healing in patients with occlusive arterial disease treated

TABLE 2. *Microcirculatory Parameters Before and After ESES**

	Before ESES	After ESES	Significance
Skin capillary density (n/mm^2)	12 ± 6	30 ± 5	$p < 0.001$
Skin capillary diameter (μm)	15.7 ± 1.8	15.5 ± 1.5	NS
Red blood cell velocity (mm/sec)	0.054 ± 0.014	0.762 ± 0.205	$p < 0.001$
Sodium-fluorescein perfused capillaries (n/mm^2)	20 ± 4	44 ± 5	$p < 0.001$
Sodium-fluorescein appearance time (sec)	72 ± 15	45 ± 9	$p < 0.001$

* Mean ± SD.
NS = not significant.



FIGS. 2A and B. Skin capillary bed after injection of sodium-fluorescein before (A) and after (B) ESES.

with ESES. Theoretically, the increase in skin perfusion can be caused by improved proximal arterial inflow, an idea supported by the significant decrease in sodium-fluorescein appearance time. The enhanced flow rate, however, did not result in a significant increase in ankle and digital arterial pressure, which might be explained by still fully dilated arterioles in this situation resulting in a "sink" for flow. An alternative explanation for the increase in nutritional skin blood flow could be redistribution of flow from muscle or bone towards the skin. ESES, however, was found to enhance skeletal muscle blood flow[17] so that shunting of blood from muscle to skin is less likely.

The patients in this study were all in the last phase before amputation. Seven of the ten patients reported long-term subjective improvement after spinal cord stimulation and were free of pain, whereas in three patients amputation was necessary. These beneficial effects are in agreement with the observations of Augustinsson et al.,[18] who used ESES in patients with ischemia based on atherosclerosis, Buerger's disease, and severe vasospastic disorders. Only 38% of the stimulated atherosclerotic patients had amputation compared with 90% in a comparable group of unstimulated patients. The amputation rate was highest in patients with ulcers and gangrene before ESES, suggesting that the treatment has no limb-saving effect when there is an established partial gangrene, which is in concurrence with the results of Broseta et al.[7]

The mechanisms by which ESES exerts pain relief and improved blood flow are still unclear. Pain is a symptom of tissue damage, caused by stimulation of A-delta and C fibers, transmitted to the cells of the substantia gelatinosa, the dorsal-column fibers, and the first central transmission (T) cells in the dorsal horn. In their "gate control theory" Melzack and Wall[19] propose that pain is determined by interaction between these three transmitting systems. The theory assumes that stimulation of the larger A fibers finally results in inhibition of the T cells. Consequently, these T cells do not react anymore to pain impulses *via* the smaller fibers. The idea of dorsal root electrical stimulation is based on the activation of the larger A fibers, leading to blockade of pain stimuli. Pain relief may release the reflex vasoconstriction that is known to occur in response to pain. Whether the sympathetic nervous system is involved is unclear. Augustinsson et al.[20] observed autonomic changes after stimulation in both patients with and without pain, raising the question whether the pain-reducing effect and the autonomic effects are a consequence of or caused by a common mechanism or two parallel phenomena. According to Melzack and Wall,[19] autonomic pathways in the intermediate columns of the grey area regulate the degree of peripheral vasoconstriction. Current spread of electrical stimulation into this area theoretically releases segmental spinal reflexes, inhibiting sympathetic fiber discharge to vessels in the extremities. Owens et al.[21] demonstrated increased infrared emission after application of nerve electrical stimulation, postulating the indirect evidence of cutaneous vasodilatation and hence, decreased sympathetic tone. This enhanced skin temperature indicates that not only nutritional flow, but also arteriovenous shunt flow increases after ESES.

Another approach to vasodilatation after electrical stimulation is described by Hilton and Marshall.[17] They demonstrated vasodilatation in the cat gastrocnemius muscle after dorsal root stimulation and postulated that this effect is due to antidromic stimulation of small diameter fibers. This dilatation was unaffected by sympathetic blocking agents, but greatly reduced by prostaglandin inhibitors. They concluded that activity in the afferent fibers of skeletal muscle produces an increase in muscle blood flow, mediated by the release of prostaglandins in muscles.

In conclusion, epidural spinal cord stimulation improves skin nutritional blood flow in patients with severe lower limb ischemia, leading to wound healing and possible limb salvage. Therefore, ESES is a promising treatment in this group of patients. Especially with our forthcoming ageing population it is extremely important to perform prospective clinical and physiologic studies to clarify the indications and to investigate the mechanisms involved.

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In Situ Tibial Reconstruction

State-of-the-Art or Passing Fancy

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To further evaluate the efficacy of *in situ* saphenous vein bypass, the authors have reviewed their experience with *in situ* bypass. Between October 1981 and December 1985, 120 *in situ* saphenous vein bypass were performed; 81 were to infrapopliteal vessels. All procedures were performed for limb salvage. The mean patient age was 74 years, and 74% were men, 57% had diabetes mellitus, 92% were smokers, and 72% had hypertension and/or coronary artery disease. All patients were evaluated by preoperative noninvasive testing and biplanar angiography. All procedures were performed by the valve incision technique. The vein utilization rate was 91%. Grafts were routinely placed into isolated tibial segments and foot vessels without evidence of a patent pedal arch. Follow-up information was obtained at 3-month intervals. Patency and limb salvage data were calculated by life-table analysis. The cumulative patency rates were 98% at 1 month, 88% at 12 months, and 82% at 50 months. These data demonstrate that the *in situ* bypass maintains an excellent patency rate and provides durable limb salvage.

IN RECENT YEARS, the *in situ* saphenous vein bypass has become increasingly popular.[1-4] Many investigators have demonstrated excellent patency rates, increased vein utilization,[1-4] as well as laboratory evidence of increased endothelial survival[5,6] and increased prostacyclin production,[6,7] which may account, in part, for observed increased patency rates. Also, many surgeons have preferred the anatomic size match-ups of the vein using the larger end to the larger common femoral artery and the smaller ends to the smaller tibial vessels instead of reversing the vein.[5,8] Most major objections to the *in situ* technique have been related to the technical nature of the procedure. Many surgeons believe that the operation is cumbersome. However, with recent advancements in instrumentation,[8] as well as the ability to map the saphenous vein before operation by B-mode ultrasound,[9,10] the procedure has become less cumbersome and more widely accepted. It is used in many centers as the primary reconstructive technique for infrainguinal arterial reconstruction.[1,5,8,11,12] The authors have reviewed their experience with 81 *in situ* bypass procedures performed to the tibial vessels to further evaluate the efficacy of the *in situ* bypass. In the past, tibial reconstructions have shown the lowest patency rates. Therefore, the authors decided that results of bypass procedures to the tibial and ankle vessels would be a reasonable method for assessing the durability of the *in situ* bypass.

Patients and Methods

Between October 1981 and December 1985, 120 *in situ* saphenous vein bypasses were performed. Eighty-one of these operations were performed to the tibial and ankle vessels. All these infrapopliteal bypasses were performed for limb salvage. Sixty-seven per cent of patients had gangrene or ischemic ulceration and 33% had rest pain. The mean patient age was 74 years, and 74% were men, 57% had diabetes mellitus, 92% were smokers, and 72% had coronary artery disease and/or hypertension. All patients were evaluated before operation with noninvasive vascular laboratory testing consisting of segmental doppler pressures and wave form analysis. All patients had preoperative biplanar angiography. Sixty-four per cent required intraoperative pre-bypass angiography to better delineate the tibial vessels. There were no attempts to locate patent pedal arches, and the only cri-

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teria used for revascularization were the presence of a segment of a tibial vessel and a foot that was deemed to have a clinically salvageable walking surface. All *in situ* bypasses were performed by the valve incision technique.[8] Before operation, the saphenous vein was evaluated by palpation and inspection. Preoperative venography was not routinely performed, and in the last 22 patients, the saphenous vein was mapped using the B-mode ultrasonic imager (Fig. 1). There were 23 bypasses performed to the anterior tibial artery, 25 to the posterior tibial artery, 13 to the peroneal artery, eight to the dorsal pedis artery, and 12 to the posterior tibial artery at or below the ankle. All patients were observed after operation at 3-month intervals with segmental doppler pressure and tracings. The minimal follow-up period was 1 month and maximum follow-up period was 50 months. The average follow-up period was 12.1 months and 27 patients were observed for more than 24 months. All patency and limb salvage data were calculated by life table analysis and were compared by Z-score analysis.

Surgical Technique

The saphenous and the common femoral artery were exposed in the infrainguinal position. The common femoral deep femoral and superficial femoral artery were isolated. The saphenofemoral junction was then dissected, and the venous tributaries to the saphenous vein were ligated. The dissection of the saphenous vein was carried out onto the common femoral vein. The distal artery and the distal saphenous vein were then dissected. Early on, the saphenous vein was entirely exposed through a continuous skin incision. However, attempts were made to leave small skin bridges, especially about the knee (Fig. 2). Systemic heparin was administered, and a curved vascular clamp was placed at the saphenofemoral junction. The saphenous vein was removed with a small rim of common femoral vein. The common femoral vein was then closed with a running 5-0 or 6-0 polyprophylene suture. One to one and a half centimeters of common femoral vein was taken along with the saphenous bulb. This allowed for an easy anastomosis to the common femoral artery. There was usually a competent valve in the saphenous bulb, which was excised under direct vision. The remaining valves were then incised early on using the valve scissors and the valvulotome. In the last half of this series, the Leather intraluminal valve cutter was used to incise the valves in all veins greater than 3 mm in diameter. After the valve incision, the proximal anastomosis was usually constructed at the common femoral artery. After flow was restored in the vein, there was usually a pulsatile column of blood seen at the distal end. At this point, no attempt was made to ligate any branches of the saphenous vein. The distal anastomosis is then constructed using a continuous 6-0 or 7-0 polyprophylene suture. Arterial flow was restored to the graft. Intraoperative postbypass angiography with needle markers was used to detect branches as well as missed or partially cut valves. Also, the sterile doppler was used with distal vein occlusion to locate remaining arteriovenous fistulae. All major side branches were ligated using double hemoclips. The sterile doppler was used to determine ankle pressure. Ankle brachial indexes were also calculated in the operating room. All skin incisions were closed in the usual manner.

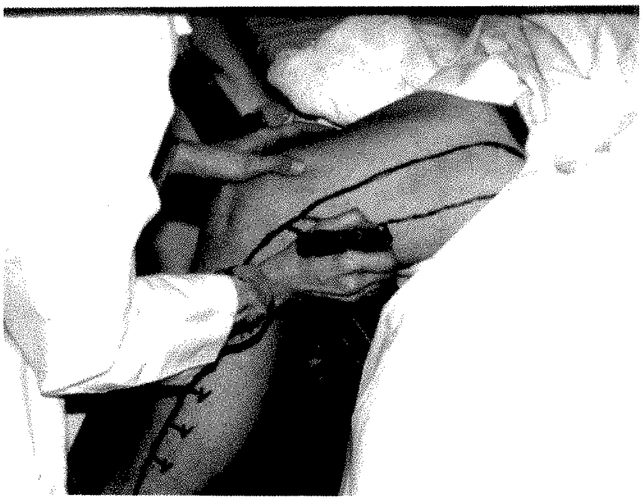

FIG. 1. B-mode ultrasound saphenous vein mapping.

Results

There were four perioperative myocardial infarctions, two resulting in death for an operative mortality rate of 2.4%. Five patients had major wound complications requiring prolonged hospitalization and there were seven

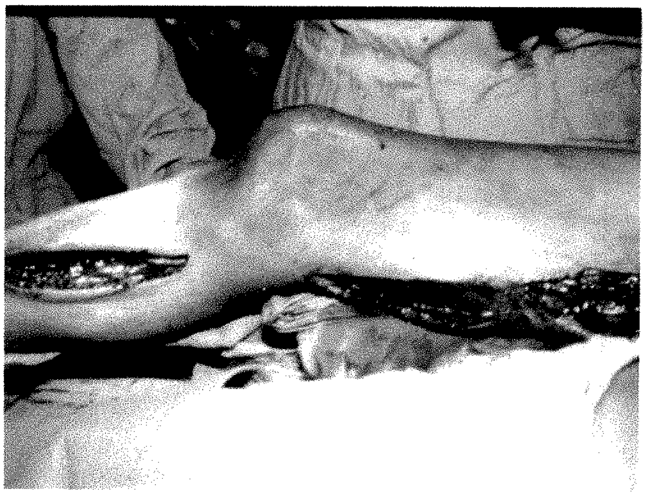

FIG. 2. Skin incision with small skin bridge.

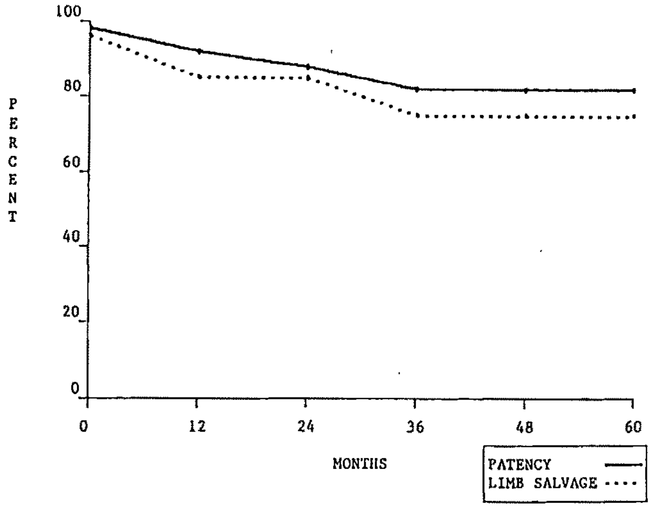

FIG. 3. Graft comparing life table analysis of graft patency and limb salvage.

minor wound complications. Five patients needed early reoperation for either missed arteriovenous fistulae or missed valve leaflets; all of these grafts were patent at the time of re-exploration. There were two patients in whom late (2 and 3 months) multiple, segmental stenosis developed in their vein bypasses. In both patients, the intraluminal valve cutter was used, and in both patients, the vein was less than 3 mm.

The cumulative patency rates were 98% at 1 month, 88% at 12 months, and 82% at 50 months (Fig. 3, Table 1). Limb salvage rates were 96% at 1 month, 85% at 12 months, and 75% at 50 months (Fig. 3, Table 2). There were 89 operations attempted and 81 completed for a vein utilization rate of 91%. The average venous diameter was 3.3 ± 0.8 mm. There were no significant differences in limb salvage and patency rates at the different anastomosis sites.

There were nine patients who required early amputation despite the presence of a well-functioning *in situ* bypass graft.

Discussion

The earliest reported *in situ* bypass was performed by Goyanes in 1906, in repairing a popliteal arterial aneurysm.[12] The idea of *in situ* bypass again emerged in the late 1950s at Saint Mary's Hospital in London, during a conversation between Carl Victor Hall, then a fellow in vascular surgery, and Charles Rob.[13] The idea of *in situ* bypass intrigued both men. Rob performed the operation by passing a blunt vein stripper retrograde down the vein, thus disrupting the valves. Carl Victor Hall returned to Oslow, and in 1962, was first to report success with the *in situ* bypass.[14] Dr. Hall performed this procedure by exposing the entire saphenous vein, and at each valve site a small transverse incision was made and the valve leaflets were directly excised.[14] The operation became popular, especially using the valve stripper in a retrograde fashion. In 1969, Barner et al. reported dismal results with the *in situ* bypass and the procedure was virtually abandoned.[15] In 1972, Leather began to reappraise *in situ* bypass, due to the continued success reported by Hall and Rostad.[16] The technique of valve incision was developed.[17] The valves were rendered incompetent by a longitudinal cut in the center of each valve leaflet, which was accomplished by passing microscissors through either the end of the vein or side branches proximal to the valves.[17] This was less trau-

TABLE 1. *Life Table Analysis Cumulative Patency*

Interval (Months)	Grafts at Risk (N)	Occlusion (N)	Withdrawn (N)	Interval Patency (%)	Cumulative Patency (%)
0–1	81	2	6	98	98
2–6	70	5	9	93	91
7–12	37	2	0	95	88
13–24	17	1	1	94	82
25–36	8	0	0	100	82
37–50	2	0	0	100	82

TABLE 2. *Life Table Analysis Cumulative Limb Salvage*

Interval (Months)	Limbs at Risk (N)	Amputation with Filled Graft (N)	Amputation with Patent Graft (N)	Interval Limb Salvage (%)	Cumulative Limb Salvage (%)
0–1	81	1	2	96	96
2–6	70	2	6	89	85
7–12	37	0	0	100	85
13–24	17	1	1	88	75
25–36	8	0	0	100	75
37–50	2	0	0	100	75

matic to the vein than the retrograde valve stripper, and was easier to perform than the individual excisions described by Hall. The scissors were modified and the retrograde valvulotome was designed by modifying a Mills valvulotome. In 1979, Leather et al. reported excellent limb salvage and patency rates with *in situ* bypass using the valve incision technique.[17,18] Since that time, there have been further advances in instrumentation. The intraluminal valve cutter was also developed.

For many years, the *in situ* bypass has been compared with the "gold standard" of the reversed saphenous vein bypass. Over time, the *in situ* bypass has gained wider acceptance. This wider acceptance has been due to improved surgical techniques, the ability to use 2–3-mm veins, and demonstrably improved patency rates. These clinical data have been supported by laboratory evidence of increased endothelial survival[5,7] and increased endothelial prostacyclin production.[6,7] In a recent report by Taylor et al., the results of reverse vein bypass were compared with *in situ* bypass, thus for the first time making the *in situ* bypass the "gold standard" for infrainguinal arterial reconstruction.[19]

For the most part, the main objections to *in situ* bypass have been the technical nature of the procedure and prolonged operating times. With the advent of the intraluminal cutter and the ability to map the saphenous vein by noninvasive B-mode ultrasonic scanning, the operation has been substantially simplified. The saphenous vein has been mapped with the B-mode ultrasonic scanner in the last 22 patients in this series. The size of the vein, location of major tributaries, and valves were determined before operation. This allowed the surgeon to decrease the length of skin incisions and to locate accurately the large branches. This in turn has led to decreased operating time. Early on, the entire vein was exposed. The authors believe that this technique was valuable for learning the techniques of valve incision. However, there is some increased morbidity associated with these long skin incisions. There were five patients in this series with major wound complications requiring prolonged hospitalizations. Four of these patients had skin flap necrosis and one had a groin infection. In seven other patients, there were minor wound complications consisting mostly of minor skin edge losses. These were treated locally and did not prolong hospitalization. It is evident that in patients with minimal skin incisions there is a decreased chance of wound complications.

The average distal vein diameter was 3.3 ± 0.8 mm. This was measured with the vein distended by blood before manipulation. Fourteen veins were less than 3 mm in diameter and over 50% of the veins were judged to be inadequate for reversed vein bypass by the old minimum criterion of 4 mm. There were no attempts to define pedal arch anatomy; however, this was commonly incomplete. In 36 patients, only one tibial vessel was available for bypass. Often, this was an isolated segmental vessel (Figs. 4 and 5).

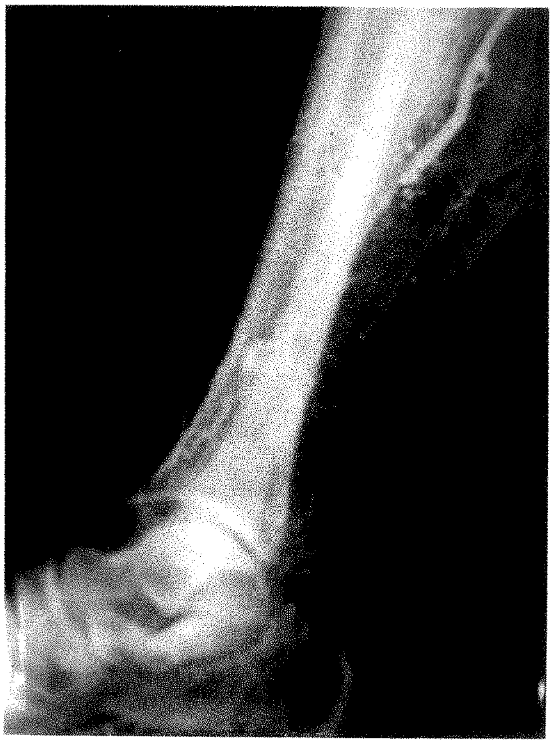
FIG. 4. Postoperative completion angiogram showing an *in situ* bypass to a distal isolated peroneal segment.

Limb salvage rates were consistently lower than patency rates. This is believed to be a function of the fact that the *in situ* graft will remain patent despite poor distal runoff. Nine patients required major amputation despite a well-functioning bypass graft. Eight of these patients were diabetics, and in this group of patients, the distal runoff was adequate to keep the graft patent but not to control the gangrene and infection.

Two patients in whom the intraluminal cutter was used later developed multiple segmental stenosis in their vein grafts. Both of these grafts failed at 2–3 months. These lesions were similar to those reported by Barner et al.,[15] and it should be noted that in both of these patients the vein diameter was 3 mm or less. Therefore, the intraluminal cutter should be used only in veins large enough to ensure that it will float freely. Recently, a 2.3-mm cutter has been developed. This cutter should be used in the smaller veins. With the advent of this additional cutter, we believe that when used appropriately, multiple segmental stenosis in the vein graft should be a decreasing problem. Despite the shortcomings in this operation of longer skin incisions and the inability to use the internal valve cutter in the smaller veins, the patency rates of 82% at 50 months and limb salvage rates of 75% at 50 months demonstrate clearly that this operation is durable. Traditionally, tibial bypass had the lowest patency rates of all infrainguinable

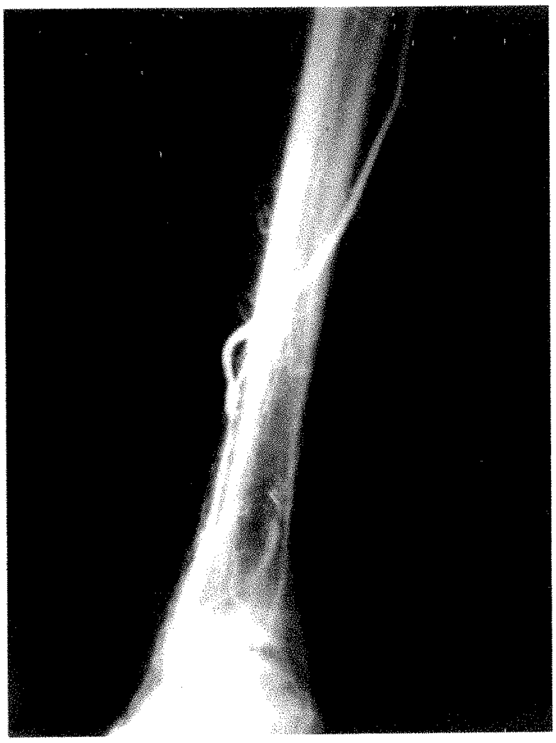

FIG. 5. Postoperative completion angiogram depicting an *in situ* bypass to a distal anterior tibial artery.

reconstructions with reversed vein and synthetic bypass grafts.[20–24] However, there does not appear to be a significant difference in patency rates between popliteal or tibial bypasses using the *in situ* technique.[1,13,25,26] It is evident from this prospective study that the *in situ* bypass offers the surgeon a reliable method for performing distal arterial reconstruction.

Therefore, in answer to the question, "is *in situ* bypass state-of-the-art or passing fancy," it is believed that this report along with others,[1–4,6,8,25,26] have shown that *in situ* bypass produces reliable results even when performed in extremely high-risk situations such as isolated tibial vessels and ankle or foot vessels. There has been increasing biochemical and structural evidence for this improved patency. With the newer techniques of valve incision, this operation is no less demanding than removing the entire saphenous vein or making composite vein grafts for harvesting arm veins or deep leg veins. Therefore, the data indicate that the *in situ* tibial bypass is a reliable method of arterial reconstruction and in many respects may be technically more rewarding than some of the reversed vein procedures. Clearly, the *in situ* bypass is no "passing fancy."

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The Patient's Appraisal of the Cosmetic Result of Segmental Mastectomy in Benign and Malignant Breast Disease

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Women's appraisal of the cosmetic result and their psychosocial adjustment after a standardized segmental mastectomy for benign or malignant breast disease was analyzed on the basis of a mailed questionnaire, which was satisfactorily answered by 263 (92%) of 285 women operated on consecutively. The overall result was favorable: 96.5% of the patients found the new appearance of their breast very good (30.7%), good (44.0%), or acceptable (21.8%). Women with a benign diagnosis ran a twofold higher risk of being discontented with the new appearance of the breast than those with breast cancer. Complications of radiation therapy, preoperative concern that the breasts are important for the appearance, and anxiousness about the cosmetic result were associated with a significantly elevated risk of being less satisfied with the outcome. The main finding that it is possible to perform a locally radical operation that is highly acceptable to the woman is relevant to the surgical management of potentially malignant mammographic lesions and also to the scientific strategies for future evaluation of breast-conserving treatment modes in malignant disease.

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As a result of the evolution in breast cancer due to early diagnosis[1-4] and controlled clinical trials,[5-7] breast-conserving operations have come to play an important part in primary treatment. It is not clear, however, from the trials for evaluation of breast-conserving treatment[5-7] which is the most preferable surgical technique. Data from the NSABP trial[7] indicate that a nonstandardized local excision cannot bring the risk of local recurrences down to an acceptable level without adjuvant postoperative irradiation. If the aim of the surgical excision is local tumor control, it is therefore logical to recommend quadrantectomy or standardized segmental resection. On the other hand, it is essential to establish whether the supposed main benefits of avoiding a mastectomy—a good cosmetic result and favorable psychosocial adjustment—can be achieved when performing a larger excision than a lumpectomy.

In attempts at early diagnosis, both in daily clinical practice and in mammographic screening programs, a number of small, radiographic lesions are observed in which a definitive diagnosis cannot be made without an excisional biopsy. To avoid possible cancer cell contamination of the wound, the lesion needs to be approached with a procedure that is both diagnostic and therapeutic. On the other hand, it is important that negative cosmetic and psychological side effects do not occur as a result of excess surgical treatment in women in whom histopathologic examination has revealed a benign lesion.

Although in earlier reports of both lumpectomy plus irradiation[8-14] and segmental mastectomy with or without irradiation[7,15,16] it has been stated that a good cosmetic result can be obtained in 70–95% of the patients, data are sparse and mainly based on evaluations by physicians or hospital staff. A considerable discrepancy between the patient's and the doctor's scoring has been found in analyses in which the patient's opinion has also been recorded.[8,14-16] Clearly the patient's own viewpoint should be the most important for an uncomplicated psychosocial adjustment.

Our aim was to investigate the cosmetic result of a segmental mastectomy in a large and consecutive series of patients, as appraised by the patients themselves. We were also particularly interested in determining whether women with benign lesions undergoing segmental mastectomy had significant side effects of the treatment.

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TABLE 1. *Characteristics of Responders and Nonresponders*

	Responders	Nonresponders
Mean age (years)	57.3	45.6
Median age (years)	59	54
Invasive cancer (N)	136	4
Cancer *in situ* (N)	19	3
Benign (N)	108	15

Materials and Methods

Patients

All women younger than 80 years who had consecutively undergone a segmental mastectomy for a benign or malignant lesion between October 1981 and May 1985 at Falun Central Hospital and Uppsala University Hospital were eligible for the study, which involved answering of a questionnaire 6 months or later after the operation. Six patients had died during the follow-up period and two were not approached because they were known to have disseminated cancer. This left 285 available patients. Of these, 192 were treated at Falun Central Hospital, which participated in the Kopparberg mammography screening program.[4,17] Twenty-two patients (8%) could not be analyzed because of mental illness and confusion (2 women), too many items unanswered in the questionnaire (1 woman), or nonresponse for unknown reasons (19 women). Table 1 shows some characteristics of the responders and nonresponders. Women with benign lesions and cancer *in situ* were grouped together in the analyses. Those with cancer *in situ* did not receive adjuvant treatment and were reassured by their doctors that they had a nonmalignant disease.

Women with invasive cancer measuring 2 cm or less on the mammogram and with no histopathologic signs of axillary metastases were treated routinely with segmental mastectomy. Most of them were randomly allocated, within a multicenter trial, to postoperative irradiation or to follow-up only.

The benign lesions and tumors *in situ* were considered before operation to be highly suspicious of invasive cancer, on the basis of a combination of clinical findings, fine-needle biopsy, and mammography. A definitive preoperative diagnosis was not, however, obtainable. Segmental mastectomy was performed in preference to incisional biopsy to ensure a radical procedure without contamination of the wound during operation if the lesion should be histopathologically malignant.

The individual record of each woman was reviewed regarding the histopathologic diagnosis, operative technique, and any surgical or radiologic complication.

Surgical Technique

The operative technique was highly standardized. During the first years of the study, a radial incision was used for all tumor locations. From 1983, tumors in the upper part of the breast were approached through a curvilinear incision. An overlying segment of skin was excised only if the tumor was palpable. Skin flaps were developed towards the periphery of the parenchyma and towards the central part of the breast. The radial segment was prepared by freeing it from the pectoralis muscle with the fascia included in the specimen. The segment was excised sharply, and included all breast tissue in an approximately 90-degree segment centered around the tumor. Generally, no attempt was made to approximate the incisional margins of the breast tissue. In all patients with invasive cancer, an axillary dissection was performed through a separate transverse incision in the axilla. A suction drain was used both for the breast and the axilla.

Any intra- or postoperative hematomas or seromas and any infections and/or delayed healing were regarded as surgical complications. In 58 (22.1%) women there were 80 surgical complications, the most common being seroma (23), hemorrhage (16), and postoperative infection (16).

Radiation Technique

A total of 68 patients were randomly allocated to receive postoperative irradiation with 54 Gy for 5 weeks in a linear accelerator giving 4–8 MV Rtg. The treatment was given 5 days per week with a tumor dose of 2 Gy per day, corresponding to a CRE value of 16.6. All postradiation erythema or inflammation requiring treatment or repeated consultations and all ulceration or severe breast edema were considered to be radiologic side effects. Eighteen patients had radiologic complications.

Questionnaire

A 24-item questionnaire concerning the socioeconomic background, cosmetic result, and psychosocial adjustment (Table 2) was issued to all women a minimum of 6 months after the operation. Women who did not answer were sent two reminders. The study was planned so that answers to specific questions in the questionnaire (see Table 2) were considered to be important outcomes (dependent variables), and the clinical data and answers to other questions as possible explanatory factors.

Statistical Methods

The women answered questions concerning the dependent variables on an ordinal scale with five different levels, and the dependent variables were tested one by one against the background factors in univariate analyses. Standard Chi square tests for homogeneity and the Walker-Duncan procedure described below were used in comparisons involving more than two levels for a variable. Results based on the Walker-Duncan procedure are reported, as the Chi square test does not make use of the ordinal character of the data. Fisher's exact test was used in 2 × 2 tables (which were obtained after combining categories with small numbers in certain cases).

In the multivariate analysis the fact that the dependent variable was ordinal made the standard regression model unsuitable. A generalization of the logistic model introduced by Walker and Duncan[18] was therefore used. The model assumes that the probability that the dependent variable y takes a value that is ≥j is given by:

$$P(y \geq j) = \frac{1}{1 + e^{-\alpha j - (\beta_1 x_1 \cdots \beta_p x_p)}} \quad j = 1,p$$

if there are p + 1 categories for the dependent variable with the "lowest" category (the most favorable outcome) as 0, where $x_1 \cdots x_p$ are background factors. The model was estimated by the maximum likelihood (ML) method (the SAS procedure LOGIST was used[19]). The large number of potentially explanatory variables necessitated the use of a stepwise inclusion of variables based on the efficient score statistic. A value of $p < 0.05$ was used as the criterion for inclusion of variables.

Parameter β_i shows the change in the log odds for $y \geq j$ with an increase in the background factor x_i provided that the other factors are unchanged. Thus a positive value of β_i implies an increased risk of having a less favorable cosmetic result with increasing values of the studied background factor. An odds ratio can be constructed from β_i as $OR = e^{\beta_i}$.

Results

Univariate Analysis

Impact of clinical data. Table 3 gives the distribution of answers to five of the main outcomes. The ratings indicating an unfavorable outcome were few. A higher frequency of women with a benign diagnosis than of those with invasive cancer found the treated breast unattractive (Table 3; p = 0.01). The distribution of ratings in the two diagnostic groups were not significantly different concerning other parameters. Age, tested as a continuous variable, did not have any significant impact on the women's appraisal of the outcome. Of the women with a medial tumor location, 13.7% reported declining sexual activity compared with 4.1% of those with a tumor in the lateral or central part of the breast. The surgeon's choice of a radial or curvilinear incision did not affect the cosmetic result as evaluated by univariate analysis.

TABLE 2. *Information Included in the Analysis*

Clinical data
  Histopathologic diagnosis
  Tumor localization
  Tumor diameter
  Surgeon
  Incision
  Intra- or postoperative complications
  Postoperative radiotherapy
  Radiologic complications
  Interval operation/inquiry
  Age

Questionnaire data: background factors
  Place of residence
  Civil status
  Number of children
  Occupation
  Education
  Whether the woman considered before operation that the breasts are important for the appearance.
  Whether there was any worry before operation about the cosmetic result.

Dependent variables
  The current appearance of the breast.
  Participation in swimming, sports, and physical training after the operation.
  Feelings about seeing oneself naked after the operation.
  Tactile sensations from the breast after the operation.
  Feelings about showing oneself naked to the family or close friends after the operation.
  Psychological distress due to the new appearance of the breast.
  Changes in sexual relations after the operation.

Impact of background factors. Among the women who were gainfully employed, 5.7% were dissatisfied with the postoperative appearance of the breast compared with 0.8% of the retired women. Neither marital status, type of employment, nor education was significantly related to any of the outcome variables (Table 2) in the univariate analysis.

Of the women who had considered their breasts as important or very important to their appearance before operation, only 33.6–37.5% reported that they did not experience unease in seeing themselves naked after the operation compared with 57.1% of those who had rated their breasts unimportant in this respect. The latter also reported less psychological distress (85.7% reported no distress at all *vs.* 62.5%). Unpleasant tactile sensations in the breast and a decreased inclination on the part of the woman to show herself naked to the family or close friends after operation were also associated with anxiousness about the cosmetic result before operation.

Multivariate Analysis

Impact of clinical data. The results of the multivariate analysis are presented in Table 4. The relationship between the few ratings indicating an unfavorable result and the background factors are shown only when odds ratio (OR) significantly (95% confidence interval) differed from 1.0. The diagnosis of benign *versus* malignant still only influenced the woman's opinion of the new appearance of her breast. Radiologic complications resulted in an approximately fivefold increased risk of

TABLE 3. *Distribution of Answers Concerning Five of the Main Outcomes**

		Invasive Cancer		Benign and Cancer *In Situ*		Total	
Question	Answer	N	(%)	N	(%)	N	(%)
What do you think of the appearance of the treated breast?	Very good	49	(36.3)	30	(24.6)	79	(30.7)
	Good	59	(43.7)	54	(44.3)	113	(44.0)
	Acceptable	25	(18.5)	31	(25.4)	56	(21.8)
	Unattractive	2	(1.5)	6	(4.9)	8	(3.1)
	Very unattractive	0	(0)	1	(0.8)	1	(0.4)
Total		135	(100)	122	(100)	257	(100)
Do you still participate in activities such as swimming, sports, physical training?	Yes, just as before	70	(51.5)	93	(75.0)	163	(62.7)
	Yes, but I dress differently	2	(1.5)	1	(0.8)	3	(1.1)
	Less than before	4	(2.9)	4	(3.2)	8	(3.1)
	Almost never or never	1	(0.7)	0	(0)	1	(0.4)
	I didn't participate earlier either	59	(43.4)	26	(21.0)	85	(32.7)
Total		136	(100)	124	(100)	260	(100)
How do you feel about seeing yourself naked since the operation?	It feels like before	50	(37.0)	54	(43.9)	104	(40.3)
	It feels almost like before	68	(50.4)	55	(44.7)	123	(47.7)
	It is a little unpleasant	16	(11.9)	7	(5.7)	23	(8.9)
	I don't like it	0	(0)	6	(4.9)	6	(2.3)
	I don't want to look at myself in the mirror any longer	1	(0.7)	1	(0.8)	2	(0.8)
Total		135	(100)	123	(100)	258	(100)
Has the changed appearance of the breast been a psychological strain on you?	No	97	(71.9)	88	(71.0)	185	(71.4)
	Just a little	25	(18.5)	20	(16.1)	45	(17.4)
	Yes, but I don't think of it every day	7	(5.2)	11	(8.9)	18	(6.9)
	Yes, a little depressing	6	(4.4)	4	(3.2)	10	(3.9)
	Yes it has made me depressed	0	(0)	1	(0.8)	1	(0.4)
Total		135	(100)	124	(100)	259	(100)
Have your sexual relations changed since the operation?	Yes, it has improved	6	(4.7)	2	(1.6)	8	(3.2)
	No, it is unchanged	70	(54.7)	91	(75.2)	161	(64.7)
	Yes, it has deteriorated	5	(3.9)	6	(5.0)	11	(4.4)
	I do not have sexual relations any longer	6	(4.7)	1	(0.8)	7	(2.8)
	I did not have sexual relations before either	41	(32.0)	21	(17.4)	62	(24.9)
Total		128	(100)	121	(100)	249	(100)

* Results are given for malignant and benign or *in situ* lesions separately; the only significant difference between the groups concerned the new appearance of the breast. The sum total figure denotes how many of the 263 questionnaires could be analyzed regarding the particular question.

reluctance to participate in swimming and to show oneself naked to the family or close friends. Women operated on with a curvilinear incision ran a higher risk (OR = 1.8) of being discontented with the new contour of the breast than those with a radial incision. Operations for tumors in the medial quadrants of the breast entailed a twofold increase in the risk of psychological distress and, parallelling the results of the univariate analysis, a fourfold higher risk of deteriorated sexual relations.

Impact of background factors. As with the univariate analysis, women working outside the home ran a 2.3 times higher risk of being discontented with the appearance of their breast after the operation than the retired women. They were also more negative about seeing themselves naked, as also were women with upper secondary school or higher education (Table 4).

Women who reported preoperative anxiety about the cosmetic result ran an approximately three times higher risk of having unpleasant tactile sensations from the treated breast, unease in showing themselves naked, or suffering psychological distress than those who did not report such anxiety. Those who had rated their breasts as important for their appearance disliked seeing themselves naked and showed high indications of psychological distress about twice as often as those who had not (Table 4).

TABLE 4. *Results of the Walker-Duncan Analysis**

Result Variable	Background Factor	OR	C.I. 95%
What do you think of the appearance of the treated breast?	Gainfully employed	2.3	(1.4–3.7)
	Benign or cancer *in situ* (vs. malignant)	2.1	(1.3–3.4)
	Curvilinear incision (vs. radial)	1.8	(1.1–3.2)
Do you still participate in activities such as swimming, sports, physical training?	Radiologic complication	5.5	(1.3–23.9)
How do you feel about seeing yourself naked since the operation?	Gainfully employed	2.3	(1.4–3.9)
	Education (upper secondary school or more, vs. lower)	3.0	(1.3–6.7)
	Breast important to appearance	2.0	(1.2–3.3)
	Radiologic complication	2.8	(1.1–7.3)
How does it feel to touch the treated breast?	Preoperative anxiousness about the cosmetic result	3.3	(1.6–6.9)
How do you feel about showing yourself naked to the family or close friends since the operation?	Radiologic complication	4.8	(1.5–15.2)
	Preoperative anxiousness about the cosmetic result	3.4	(1.3–8.8)
Has the changed appearance of the breast been a psychological strain on you?	Preoperative anxiousness about the cosmetic result	3.3	(1.5–7.1)
	Tumor in medial part	2.2	(1.2–4.0)
	Breasts important to appearance	2.0	(1.1–3.9)
Have your sexual relations changed since the operation?	Tumor in medial part	4.0	(1.5–10.6)

* The statistically significant results are given as the odds ratio (OR) with 95% confidence limits (C.I. 95%) for reporting stepwise a less satisfactory result for the seven main outcome variables. Compare Table 2 for alternative answers given for five of the questions.

Discussion

The women in this study were recruited from a comprehensive and unselected population. Facilities for private care of breast cancer patients were not available in the two counties. The same diagnostic and therapeutic strategy, including the surgical technique, was used and the two surgical clinics participated in the same clinical trial for breast-conserving therapy. Few eligible women were excluded because of death or disseminated disease and a high response rate (92%) was achieved. Nonresponders were slightly younger and predominantly operated on for benign disease and probably were not as concerned about the disease and the cosmetic outcome.

Once local tumor control has been achieved, the main goal of breast-conserving therapy as compared to mastectomy is a good cosmetic result in conjunction with a favorable psychosocial adjustment. The study design allowed us to assess the outcome from this perspective. The overall cosmetic result was good and the social life and sexual relations of the patients were largely unaffected. If the cosmetic result is one determinant of psychiatric problems reported after breast cancer therapy, our results indicate that its impact is weak after a segmental mastectomy. Indeed, the overall number of side effects was so low that prudence is advisable in interpreting the results concerning single explanatory variables. Some of the statistically significant differences could have occurred by chance.

We were unable to define particular preoperative characteristics entailing a high risk of developing a strong negative reaction after operation. Two psychological factors, however, seemed to be associated with a poor outcome, namely preoperative concern about the cosmetic result and a high evaluation of the breasts for personal appearance. This finding is in accordance with risk factors found for psychological distress after mastectomy.[20] It is possible that these are important prognostic factors, but the observation must be interpreted cautiously, since it could be due to artefacts of recall bias. Women with a poorer cosmetic outcome may remember their preoperative uneasiness better.

One major finding was that although women with a benign diagnosis gave poorer ratings for the appearance of the breast, they did not report more psychological distress or other negative outcomes. The type of incision used did not have the importance for the patients' appraisal of the result suggested in other studies.[8,11,12] However, the operations analyzed here were performed with a standardized technique in patients who were all presumptive candidates for a prospective randomized trial. This probably tends to unify and raise the standards of treatment. Complications of radiotherapy impaired the cosmetic result even when surgical complications were taken into account in the multivariate analysis.

In studies on psychological consequences of mastectomy, divorced women and women in an unhappy marriage reacted more often with depression.[21,22] In the current study, however, being single or divorced did not increase the risk of an unfavorable assessment of the cosmetic result.

The significance of the only major argument against a segmental mastectomy as compared to lumpectomy, which is an inferior cosmetic result, is contradicted by the results of this study. It is of great strategic importance for the treatment of small lesions of the breast that a locally radical operative procedure can be done without serious psychological side effects. The routine acceptance of such an operative procedure would confer two major benefits. First, in those cancer patients where breast-conserving therapy is appropriate, it would avoid time spent in evaluating minimal or nonstandardized surgical techniques. These appear to give inferior local control of disease as indicated by the high rate of recurrences located primarily to the site of earlier surgery.[7,23,24] It would be more important, having accepted such a procedure as standard, to critically assess the role of postoperative radiotherapy in local tumor control. Second, in a screening situation it would be preferable, provided that the specificity of the screening is the same as that in the current setting,[4] to decide on a radical excision of lesions suspected, but as yet not proven, to be cancerous. This would avoid contaminating the wound if the lesions were histopathologically malignant.

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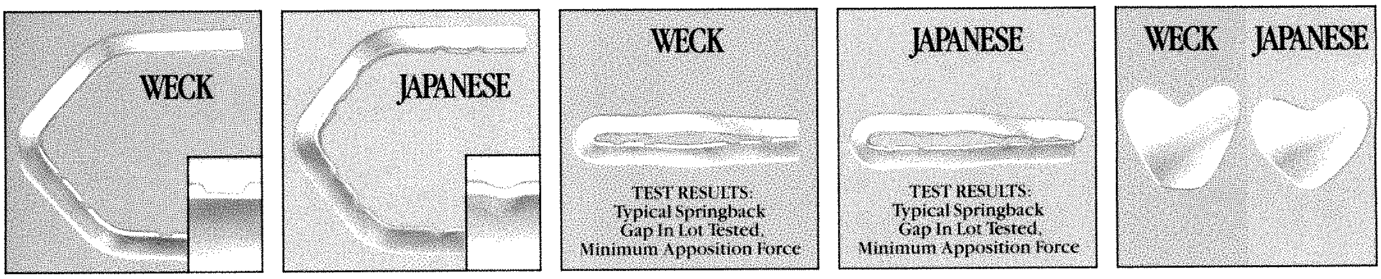
Hemoclip® ligating clips are made for blood vessels.

That sounds obvious, but it's not to everyone.

It's not easy to make ligating clips that are finely balanced between strength and malleability–two desirable ligating clip properties.

But in a quarter-century of manufacture, Weck has learned to do the job on this key implant device as no one else has.



The Hemoclip® ligating clip is coined with distinct rectangular transverse grooves, designed for longitudinal gripping power. Clip wire is processed metallurgially for malleability in closure. The Japanese imitation clips have shallow-drawn wire, and smaller, rounded transverse grooves. Deeper Hemoclip® wire shape aids retention in Weck appliers. (Typical closure illustrated from independent study.)

But now there's a problem you should be aware of. Some U.S.-based companies have begun distributing–not manufacturing–Japanese imitations of the Hemoclip® ligating clip. These clips are not the product of Weck manufacturing expertise and the technical performance of these clips is simply not the same as that of Hemoclip® ligating clips, an exclusive Weck product.

They may look the same, but they're not.

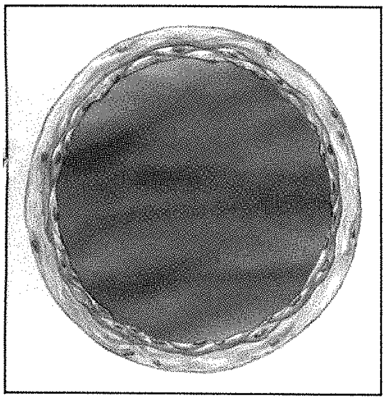
The recently-introduced Japanese clips look the same as Hemoclip® ligating clips to the naked eye. But a recently completed independent lab study of sample quantities of clips confirms Weck's own observation of substantial differences in closure properties between the Japanese clips and Weck clips.

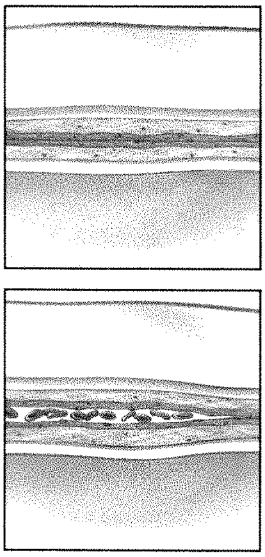
Vessel walls may be as thin as one-twelfth of vessel diameter.

Veins, in contrast to arteries, have very thin walls. When you consider that the vein tributaries ligated in surgery are sometimes one millimeter in diameter or smaller, with combined vessel walls as small as seven-thousandths of an inch (178 microns), according to animal studies on comparable vessels, you can appreciate the functional importance of differences in closure gap.

Arterial tributaries can be tiny, too, and although their walls are generally thicker than vein walls, arterial pressure is higher than venous pressure.

It seems prudent to employ ligating clips which offer the response and clip-closure performance Weck usage has established in your surgery.





ABOVE. A vein tributary of 1mm can have a combined wall thickness of just seven-thousandths of an inch (178 microns), according to animal studies. RIGHT. A ligating clip that demonstrates greater springback than the clip you have regularly used for such vessels may be more likely to leave a closure gap larger than the vessel-wall thickness of a tiny vessel.

Weck's titanium clip vs. their titanium clip. A 23-27% difference.

Examine the chart for a visual representation of the difference in closure springback an independent research firm discovered between a set of Weck titanium medium-size clips and a set of Japanese titanium medium-size clips obtained directly from U.S. distributors of those clips. Both sets of clips were closed in Weck appliers through use of force-control devices.

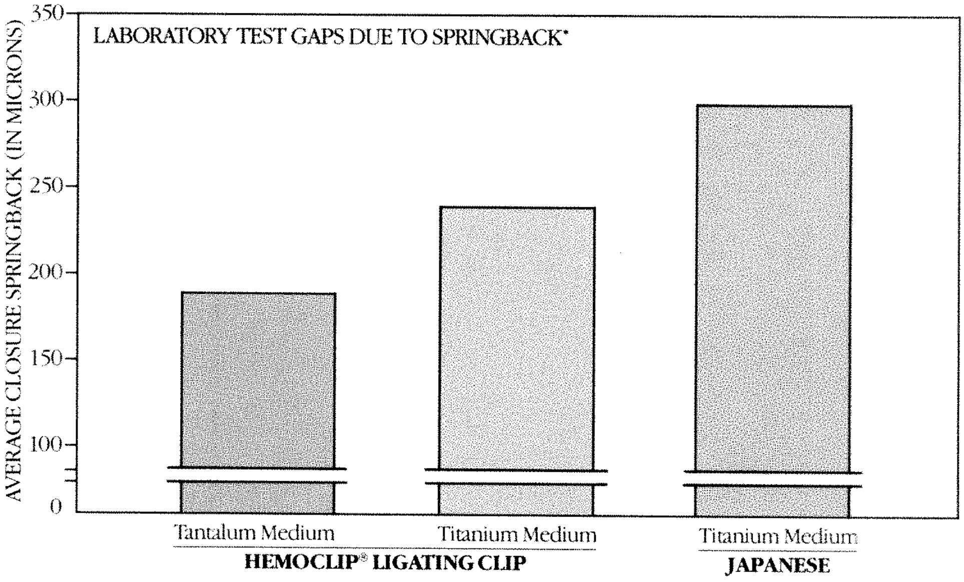
Closure of two sample sets of 25 Japanese titanium medium clips at forces adequate to achieve initial complete touching along clip legs resulted in closures of about 12 thousandths of an inch (305 microns) for the Japanese clips, 23-27% larger than the Weck titanium clip closure gap.

Weck's tantalum clips vs. their titanium clips. A 56% springback difference.

The comparison of Japanese titanium with Weck tantalum clips is even more important.

The Japanese companies make only titanium clips, and so they have sold hard on the benefits of titanium.

Tantalum is a softer material known for excellent clip closure. And the study revealed 56% and 61% larger mean closure gaps after springback for two sets of Japanese titanium clips, a ringing endorsement of the closure advantages of the Weck tantalum clips tested.



An independent lab study on two sample sets of 25 Japanese imitation clips vs. Weck clips found that the Japanese medium-size clips, closed to initial complete touching of clip legs, evidenced mean closure gaps, due to springback, 23-27% larger than Weck medium-size titanium clips, and 56-61% larger than Hemoclip® tantalum clips from Weck. Other sizes produced similar results. (Closure gap in microns-one micron = one thousandth of one millimeter).

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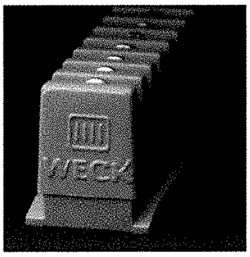
*Stronger closure forces would likely be employed during actual surgery cases.

The comparison was similar for Weck stainless vs. Japanese titanium, with the stainless scoring substantially smaller gaps after springback.

Odds are, if you are using Weck clips you are accustomed to tantalum or stainless steel clip closure, because the vast majority of Weck accounts use these two metals.

And a new Weck-funded NMR major-university study indicates that magnetic deflection of tantalum clips is negligible, just as it is for titanium clips. So if your local competitive salesman distributing Japanese clips tries to convince you that titanium clips are exclusively acceptable for NMR magnetic deflection in preference to tantalum, we suggest you cite the new Weck-sponsored university study.

Look for the Weck name on the cartridge.



To visually and quickly confirm that you really are using Weck clips, look at the end of the clip cartridge. If you are using Weck clips, you should see there the Weck name molded into the plastic. The Weck name is your assurance of genuine Hemoclip® clip processing experience and knowledge.

Perfection In A Surgeon's Hand.™ WECK®
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If you would like more detailed information on any of the points covered here, write Edward Weck Incorporated, P. O. Box 12600, Research Triangle Park, NC 27709. 1-800-334-8511. In NC 1-800-672-6583.

The Effect of Hemorrhage and Resuscitation on Serum Levels of Immunoreactive Atrial Natriuretic Factor

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To determine if atrial natriuretic factor (ANF) might have a role in blood volume regulation during hypovolemia, the serum level was measured before and after hemorrhage and resuscitation (RESUS) in a porcine shock model. Hemorrhage of 40% of the blood volume produced significant ($p < 0.01$) decreases in mean arterial pressure, central venous pressure, and cardiac output and a significant increase in heart rate (HR), plasma renin activity, and catecholamines ($p < 0.01$). Hemorrhage was also associated with a significant increase in ANF ($p < 0.05$). All parameters except HR returned to baseline values with RESUS. The rise in ANF associated with moderate hemorrhage was unexpected, but may have been due to the profound tachycardia or decreased degradation during shock. Sodium excretion and urine flow increased significantly with RESUS without an associated increase in ANF, suggesting that ANF may not be involved in the early phase of postresuscitation diuresis.

ATRIAL NATRIURETIC FACTOR (ANF), a peptide produced by mammalian atrial cardiocytes, may play a major role in fluid and electrolyte homeostasis, control of vascular tone, and regulation of blood volume.[1] It is known to have potent natriuretic, diuretic, and vasorelaxant properties in euvolemic and hypervolemic states.[2,3] Stimuli for the release of ANF include tachycardia,[4,5] atrial distention,[6] and hyperosmolarity.[7] Elevated serum levels of ANF, determined by radioimmunoassay (immunoreactive ANF [irANF]), have also been found in patients with congestive heart failure.[8] There has been no investigation of irANF during hemorrhagic hypovolemia, a physiologic state characterized by major shifts in fluids, significant alteration in vascular tone, and sodium and water retention. There also has not been any exploration of a possible role for ANF in the marked diuresis and natriuresis that occurs after resuscitation from hypovolemic shock. To determine if ANF might be involved in blood volume regulation during and after shock and resuscitation, we measured serum levels of irANF before and after hemorrhage and resuscitation in a porcine model of severe hypovolemic shock.

Materials and Methods

Twelve mature swine (5 males, 7 females) weighing 28–34 kg underwent general endotracheal anesthesia with halothane 0.5–1% for placement of catheters for blood sampling and hemorrhage and for measuring mean arterial pressure (MAP), central venous pressure (CVP), pulmonary artery wedge pressure (PWP), and cardiac output (CO) by thermodilution.[9] A catheter was surgically placed in the bladder for obtaining urine samples and measuring output. After recovery from anesthesia, the animals were returned to their cages. After an overnight fast, the unanesthetized, fully awake pigs were returned to the study area and allowed to acclimate to their surroundings. Baseline (BL) measurements of heart rate (HR), MAP, CVP, PWP, CO, and urine output (UO) were recorded. Serum and urine samples were obtained for measurement of sodium and creatinine concentration and osmolarity. Sodium concentration in the urine and serum was determined by flame photometry, creatinine by the ASTRA Ideal System picric acid rate reaction (Beckman Instruments, Fullerton, CA), and osmolarity by vapor pressure changes.[10] Cardiac stroke volume (SV) was calculated by dividing the CO by the HR. Urine flow rate was calculated by dividing

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TABLE 1. *The Effect of Hemorrhage and Resuscitation on Hemodynamic Parameters* (Mean ± SEM)*

Parameter	Baseline	Immediately after Hemorrhage	Immediately after Resuscitation	24 Hours after Hemorrhage (D_1)
MAP (mmHg)	106 ± 2	53 ± 6*	101 ± 5	102 ± 4
HR (beats/min)	113 ± 11	187 ± 13*	145 ± 10†	120 ± 8
CO (L/min)	3.3 ± 0.2	1.6 ± 0.2*	3.6 ± 0.1	3.9 ± 0.2*
SV (ml/beat)	31 ± 3	8 ± 1*	26 ± 2	34 ± 2
PWP (mmHg)	9.3 ± 0.8	7.2 ± 1.2	10.5 ± 0.8	8.9 ± 0.7
CVP (mmHg)	4.0 ± 0.9	0.4 ± 1.2*	3.8 ± 0.9	3.4 ± 0.8

All values compared with baseline: * $p < 0.01$; †$p < 0.05$.

the UO by the duration in minutes of the interval of collection. Additional serum was collected in chilled plastic tubes, immediately placed on ice, centrifuged at −4 C, and the supernatant stored at −70 C for the later determination of irANF and plasma renin activity (REN) by radioimmunoassay (RIA),[11,12] and epinephrine (E) and norepinephrine (NE) by radioenzymaticassay (REA).[13] After the BL measurements and sampling were complete, the pigs were bled 40% of their calculated blood volume[14] over 30 minutes. The shed blood was centrifuged for later administration as packed red blood cells (PRBC). After an additional 30 minutes, resuscitation (RESUS) was begun with crystalloid solution, either Ringer's lactate (RL:sodium = 130 mEq/L; osmolarity = 274 mOsm/L) or hypertonic sodium lactate (HSL:sodium = 250 mEq/L; osmolarity = 512 mOsm/L). After an additional 60 minutes (120 minutes after the initiation of hemorrhage), shed PRBC were administered to return the hematocrit to approximately two thirds of the BL value, and additional crystalloid, RL or HSL, was administered to maintain the CVP at BL value. Measurements were repeated hourly for 24 hours. Serum hormone determinations and serum and urine sodium, creatinine, and osmolarity determinations were repeated at the completion of hemorrhage, immediately after RESUS and 24 hours after hemorrhage. Resuscitation was believed to be complete when the MAP and CVP were stable at BL values. The animals were given nothing orally during the 24-hour study. At the completion of the study they were returned to their cages and given food and water *ad libitum.*

The irANF was measured using a modification of the radioimmunoassay of Gutkowska et al.[11] and Napier et al.[15] The assay sensitivity was 40 pg/ml and the within-assay coefficient of variance was 5%. Specimens from a single animal were run with the same assay.

The assay is specific for ANF and closely related peptides. The antibody used does not cross-react with somatostatin, oxytocin, or vasopressin. The antibody does cross-react with longer peptides that contain the ANF molecule such as atriopeptin I (3%) and atriopeptin II (27%). It also cross-reacts with fragments of ANF so that the peptide containing amino acids 18–28 shows a 57% cross-reactivity. However, none of these related peptides were found to be present in significant quantities in the blood of any animal.

Comparisons were made using the Student's t-test for paired and unpaired data, one-way analysis of variance, and the Wilcoxen two sample rank sum test. All computations were performed using the BMDP statistical analysis software and the Clinfo Database Management System (University of California Press, Berkeley, CA). Significance was attributed to a value of $p < 0.05$. All values are expressed as mean ± SEM.

Results

The swine were bled an average of 883 ± 24 ml, or 28.3 ± 0.1 ml/kg. This degree of hemorrhage produced significant decreases in CO, SV, MAP, and CVP, and a significant increase in HR (Table 1). Resuscitation required a volume of 2507 ± 294 of RL or 1575 ± 132 of HSL ($p = 0.01$) and 157 ± 13 ml of packed red blood cells. This returned all of the hemodynamic parameters to a value equal to or greater than the BL value. The HR was significantly elevated after resuscitation, but was not significantly different than BL at D_1 (Table 1).

Hemorrhage produced significant elevations in all of the hormones. The increase was greatest for the catecholamines and REN, reflecting the severity of the model (Table 2). The 10-fold increase in REN indicated that the hemorrhage had severely contracted the extracellular fluid volume. There was a significant increase in irANF associated with hemorrhage (Fig. 1). The 34% increase in irANF was less pronounced than the elevations in the other hormones. After fluid resuscitation, REN and irANF had returned to BL, whereas E and NE were still elevated. All hormone concentrations returned to BL by 24 hours after hemorrhage, except irANF, which was significantly lower at D_1 than at BL.

The evaluation of renal function during hemorrhage was made on urine samples collected over 1 hour beginning with the initiation of hemorrhage and ending just before the start of resuscitation. Generally, urine output in all animals was unchanged from BL during the first

TABLE 2. *The Effect of Hemorrhage and Resuscitation on Plasma Catecholamines and Renin Activity (Mean ± SEM)*

Hormone	Baseline	Immediately after Hemorrhage	Immediately after Resuscitation	24 Hours after Hemorrhage (D_1)
Epinephrine (pg/ml)	182 ± 47	9600 ± 2488*	335 ± 70†	253 ± 76
Norepinephrine (pg/ml)	427 ± 48	8140 ± 2557*	788 ± 180†	442 ± 38
Renin (mg/ml/h)	1.6 ± 0.3	17.1 ± 2.2*	1.4 ± 0.2	1.3 ± 0.2

All values compared with baseline: * $p < 0.01$; †$p < 0.05$.

20 minutes of hemorrhage, but decreased sharply thereafter. Urine output approached zero in all animals during the last 10–15 minutes of the collection period. Hemorrhage and resuscitation produced major changes in renal function (Fig. 2). Hemorrhage caused a decrease in creatinine clearance, which was reversed with resuscitation. Urine flow decreased with hemorrhage, but increased significantly with resuscitation and remained elevated on D_1. Sodium excretion during the 1-hour interval of collection was unchanged from BL, but decreased with the fall in urine flow during the 30-minute interval before initiating RESUS. Sodium excretion increased significantly with resuscitation and continued to increase on D_1.

Crystalloid was administered throughout the first 24 hours to maintain the CVP at BL value resulting in a net accumulation of sodium (305 ± 32 mEq) and water (1560 ± 296 ml) by D_1 (Fig. 2). The amount of sodium required to resuscitate the animals and to maintain hemodynamic stability was approximately 2.2 times the amount of sodium lost.

The finding of a significantly increased irANF with hemorrhage was unexpected. We postulated that the tachycardia that occurred with hemorrhage may have caused the increased release of irANF as described by others.[4,5] To investigate this possibility, we attached

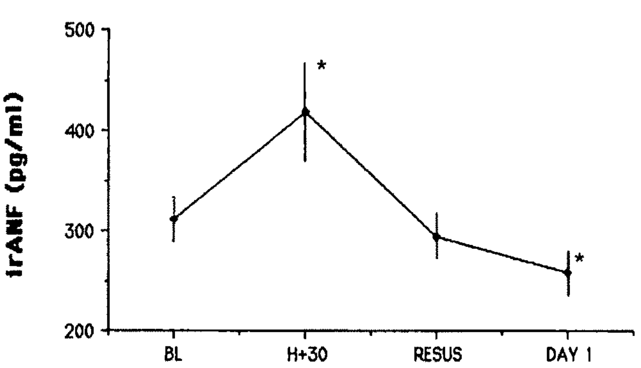

FIG. 1. The effect of hemorrhage and resuscitation on serum levels of irANF. Hemorrhage was associated with a significant increase in irANF. BL = baseline; H + 30 = immediately after hemorrhage; RESUS = immediately after resuscitation; DAY 1 = 24 hours after hemorrhage. Bars indicate SEM. All values compared to BL, *$p < 0.05$.

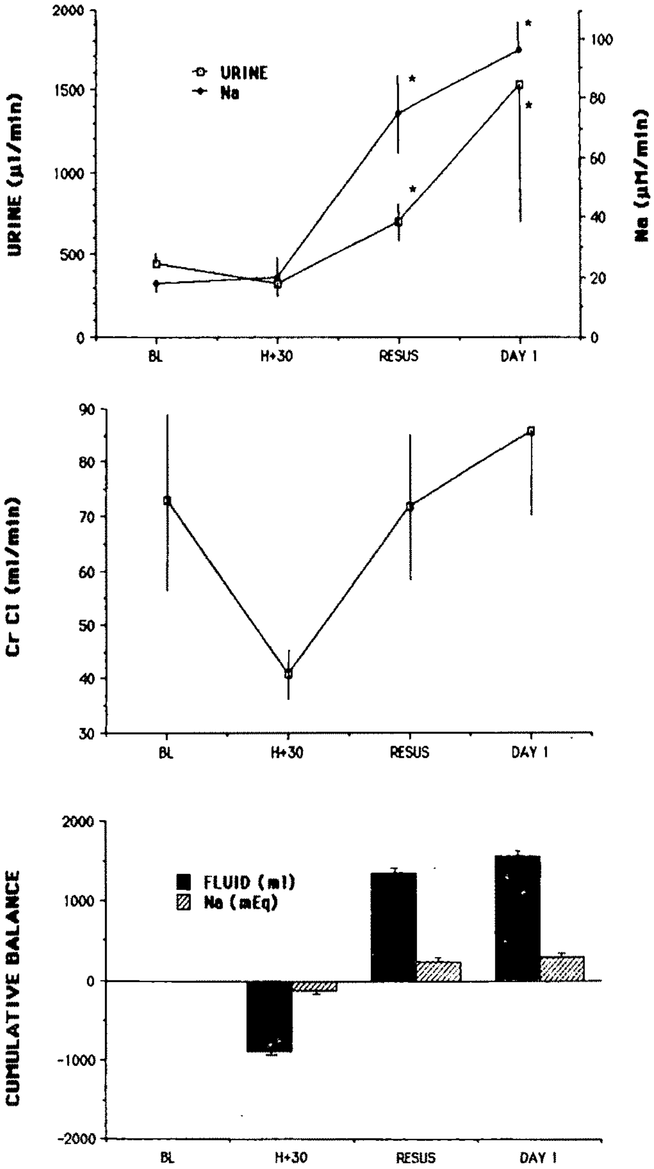

FIG. 2. The effect of hemorrhage and resuscitation on renal function. Top panel shows urine flow (URINE) and sodium excretion (Na). Middle panel shows creatinine clearance (Cr Cl). Bottom panel shows the cumulative fluid and sodium balances. Urine flow and Cr Cl fell with hemorrhage. Cr Cl normalized with resuscitation while urine flow and sodium excretion increased significantly. BL = baseline; H + 30 = immediately after hemorrhage; RESUS = immediately after resuscitation; DAY 1 = 24 hours after hemorrhage. Bars indicate SEM. All values compared to BL; *$p < 0.05$.

TABLE 3. *The Effect of Atrial Pacing on irANF Levels (Mean ± SEM)*

	Baseline	During Pacing
HR (beats/min)	111 ± 15	170 ± 8*
CO (L/min)	2.6 ± 0.7	2.1 ± 0.6
CVP (mmHg)	7.8 ± 1.8	7.0 ± 2.4
ANF (pg/ml)	281 ± 67	528 ± 96*

All values compared with baseline: * $p < 0.05$.

TABLE 4. *The Effect of Rapid Fluid Infusion on irANF Levels (Mean ± SEM)*

	Baseline	After 2-L Infusion
HR (beats/min)	124 ± 7	134 ± 14
CO (L/min)	3.5 ± 0.4	6.3 ± 0.9*
CVP (mmHg)	4.4 ± 1.2	14.8 ± 2.9*
ANF (pg/ml)	418 ± 51	1424 ± 530*

All values compared with baseline: * $p < 0.05$.

pacing wires to the right atrium with surgical clips through a median sternotomy under a general anesthetic (halothane 0.5–1.0%) and measured CO, CVP, HR, and irANF after the sternotomy and placement of the pacing wires and during atrial pacing in five additional pigs. Pacing produced significant increases in HR and irANF, whereas CO and CVP decreased slightly (Table 3). The amount of increase in irANF with pacing was variable in each individual pig (Fig. 3).

To determine if the swine exposed to severe shock and allowed to recover could release irANF in response to volume loading, we restudied five animals 96 hours after the completion of shock experiments. Fluid (1–2 L of crystalloid) was rapidly infused into the central circulation to produce at least a threefold rise in CVP. Cardiovascular parameters and irANF were measured before and at the end of the fluid infusion. Rapid fluid infusion significantly increased the CO, CVP, and irANF (Table 4). Although the HR increased with fluid infusion, the rise was not significant. The individual increases were more pronounced with fluid infusion than those observed with atrial pacing (Fig. 4). A pronounced diuresis followed the fluid infusion and the irANF elevation. For the 10-minute interval immediately after the infusion, the urine flow rate increased to 3.1 ± 1.7 ml/min and for the initial 30 minutes the average urine output was 2.5 ± 0.5 ml/min.

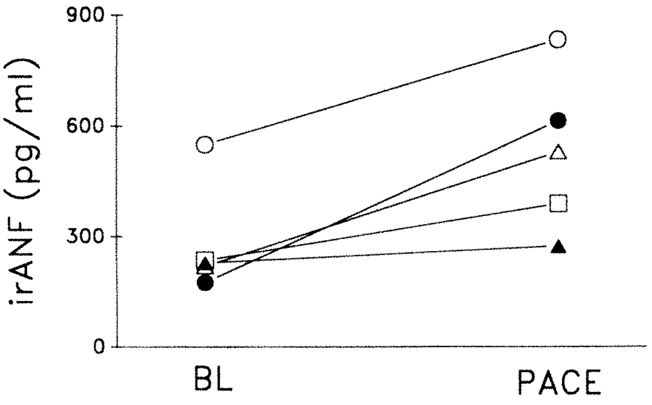

FIG. 3. The effect of atrial pacing on serum levels of irANF in five swine. The irANF increased with pacing, but the amount of increase was variable. BL = baseline; PACE = during pacing.

Finally, we compared the irANF levels in animals resuscitated with RL with those resuscitated with HSL to determine if serum osmolarity or sodium concentration affected the levels of irANF after hemorrhage and resuscitation (Table 5). There were significant differences between the RL and HSL groups in serum sodium and osmolarity at RESUS and at D_1. However, there was no difference between the groups in the irANF level measured at these intervals.

Discussion

A relationship between the heart and the kidney in the control of blood volume has been suspected for 40 years.[16] This relationship was confirmed when de Bold and co-workers demonstrated that extracts of rat atria produced a profound natriuresis and diuresis.[17] Subsequent work has shown that the atrial extracts have vasorelaxant properties as well.[18,19] The active material appears to be located in the paranuclear region of the cardiocyte[20] and to consist of small related peptides that have now been identified, sequenced, and synthesized.[21] Release of these peptides has been linked primarily to atrial distention,[6] usually associated with increased cardiac filling pressures.[8] Other possible stimuli for release include hyperosmolarity[7] and tachycardia.[4,5] Since tachycardia and wall tension induced by atrial stretching are believed to release ANF, it seemed that the release mechanism could be further elucidated by measuring irANF in a physiologic state characterized by tachycardia and hypovolemia.

We selected a model of severe hemorrhage (40% of the blood volume) over a short period (30 minutes). This model has an expected mortality rate of approximately 20%.[22] We delayed the initiation of resuscitation for 30 minutes to conform to the usual clinical scenario. The severity of this model was reflected in the cardiovascular and humoral responses. There were significant decreases in CO, SV, MAP, and CVP and significant increases in E, NE, and REN.

It was unexpected that hemorrhage would result in a significant increase in irANF. Although this increase was relatively small compared with the catecholamines and renin, the increase was notable in view of the profound hypovolemia. One explanation for this increase is that it was due to the rise in heart rate. Others[4,5] have observed an increase in irANF associated with atrial tachycardia. However, in those experiments and observations, atrial wall tension may have contributed to the rise in irANF since there was an associated increase in either right atrial pressure or CVP. In the experiments described here, there was a significant decrease in CVP associated with tachycardia; therefore, a rise in atrial wall tension is unlikely to have contributed to the observed increase in irANF. When atrial pacing was induced in euvolemic swine, the associated increase in irANF was greater than that observed with tachycardia and a decreased CVP in the hypovolemic swine. Rapid fluid infusion in the euvolemic swine was associated with a sharp increase in CVP and was associated with the greatest increase in irANF. Tachycardia associated with increases in wall tension may act synergistically to increase irANF. The release of irANF in these swine had the anticipated effect of increasing urine flow (and, presumably, sodium excretion). However, as Goetz et al.[23] have pointed out, the increase in urine flow may be entirely or partly due to the effects of wall tension mediated by vagal afferents.

The release of irANF in severe hemorrhage could have been related to the presence of other hormones associated with the shock state. Clearly, catecholamines could have been responsible since the irANF increase coincided with increases in E and NE. However, irANF had returned to BL value at RESUS when E and NE were still significantly elevated. Possibly, irANF could have been released in association with the release of vasopressin. Vasopressin is known to be released after hemorrhage[24] and has been observed to increase irANF in euvolemic rats.[25] In addition, some have suggested the possibility that irANF and vasopressin are functional antagonists and exist in a negative feedback relationship.[25]

The observed increase could also be explained by a decrease in the degradation of the peptide associated with an unchanged basal secretion rate that was unaffected by the contraction of the plasma volume. This is a plausible explanation of our observations since the magnitude of decrease in the vascular volume (40%) was similar to the magnitude of increase in irANF (34%). A basal secretion rate unaffected by severe hemorrhage suggests that ANF may have a physiologic role in the response to hemorrhage, perhaps as an antagonist to the endogenous vasoconstrictors released during shock. Indeed, ANF has been shown to antagonize NE-induced vasoconstriction[26] and to reverse NE-induced acute renal failure.[27]

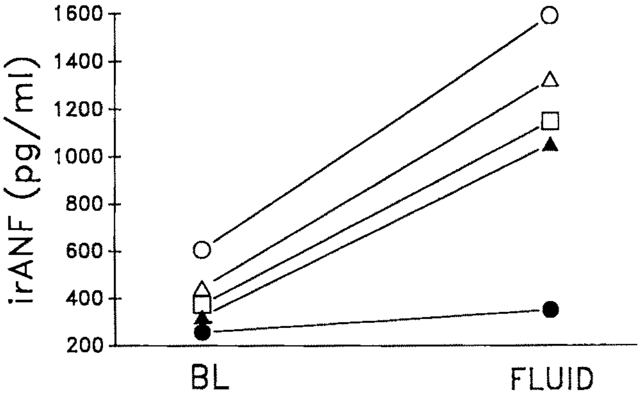

FIG. 4. The effect of rapid fluid infusion on serum levels of irANF in five swine. The irANF increased with fluid infusion. BL = baseline; FLUID = immediately after infusion.

We observed no difference in irANF in swine resuscitated with an isotonic solution (RL) and those resuscitated with a hypertonic solution (HSL). There were significant differences between the two groups in serum sodium and serum osmolarity at RESUS and D_1, but there was no difference between the groups in irANF measured at those times. This suggests that, within the range of our observations (serum sodium: 140–150 mEq/L; serum osmolarity: 285–301 mOsm/L), serum sodium and serum osmolarity do not appear to affect the release of irANF. However, there was only a change of 10% in these parameters during the study and this may have been of insufficient magnitude to affect ANF release. On the other hand, an increase in serum osmolarity of less than 2% can result in a doubling of serum vasopressin levels.[28] If osmolarity is operant in ANF release, the sensitivity of the mechanism appears to be far less than that for AVP release.

Resuscitation normalized the physiologic parameters and returned irANF and REN to BL. By 24 hours after hemorrhage, E and NE had returned to BL and ANF was significantly lower than BL value. This occurred at a time when urine flow and sodium excretion were significantly increased from BL. These results suggest that ANF is not the stimulating factor in the diuresis and natriuresis observed in the postresuscitation period.

TABLE 5. *Comparison of Serum Sodium and Osmolarity and irANF Levels in Animals Resuscitated with RL and HSL (Mean ± SEM)*

	Immediately after Resuscitation		24 Hours after Resuscitation	
	RL	HSL	RL	HSL
SNa (mEq/L)	140 ± 2	150 ± 2*	145 ± 3	153 ± 2†
SOsm (mOsm/L)	286 ± 4	300 ± 4*	284 ± 3	301 ± 5*
ANF (pg/ml)	279 ± 25	308 ± 26	259 ± 32	256 ± 14

Comparisons made between groups (HSL *vs.* RL): * $p < 0.01$; † $p < 0.05$.
SNa = serum sodium concentration.
SOsm = serum osmolarity.

However, our study encompassed only the first 24 hours after hemorrhage, a period marked by a positive sodium and water balance. It is certainly possible that ANF could be involved in the later stages of salt and water excretion, especially when mobilization of fluid is associated with a rise in the CVP. Swine infused with sufficient crystalloid to elevate the CVP 96 hours after the shock experiments had a significant increase in irANF and urine output. It is important to study the potential role of ANF in postresuscitation diuresis further since the salt and water retention after shock and trauma may be detrimental to cardiac and pulmonary function.[29]

Acknowledgments

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Neuroendocrine (Merkel Cell) Carcinoma of the Skin

Its Natural History, Diagnosis, and Treatment

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Over 400 cases of neuroendocrine (Merkel cell) carcinoma of the skin (NCS) have been reported. This tumor continues to pose problems in diagnosis and effective treatment for physicians unfamiliar with its biological characteristics. Reported here are five additional cases of NCS and the literature for this rare neoplasm is comprehensively reviewed. An early and accurate diagnosis is made possible by combining clinical presentation with results of histologic study, immunoperoxidase staining for neuron-specific enolase (NSE), epithelial membrane antigen (EMA), cytokeratins, and electron microscopy. NCS is an aggressive tumor. Depending on the length of follow-up, up to 40% of tumors locally recur, 55% develop regional nodal metastases, and 36% undergo distant metastasis. Survival is sex, but not age, dependent, with an overall 2-year survival rate of 72% (males 58% *vs.* females 79%). No standard procedure for initial and/or follow-up treatment for NCS exists. The authors recommend that NCS be treated, whenever possible, using the same rationale as applied for the treatment of squamous cell carcinoma of the skin.

IN 1972, TOKER COINED THE TERM "trabecular carcinoma" to describe a poorly differentiated carcinoma of the dermis and subcutaneous tissue identified in five elderly people.[1] To date, over 400 cases of this primary cutaneous neoplasm have been reported under a variety of terms[2–65] that include: neuroendocrine carcinoma of skin,[6,8] Merkel cell tumor or carcinoma,[9] primary small-cell carcinoma of the skin,[10] APUDoma,[11] extra-pulmonary carcinoma of the skin,[49] and endocrine carcinoma of the skin.[50] The term neuroendocrine carcinoma of the skin (NCS) is preferable and describes the histologic, ultrastructural, and immunohistochemical features of the tumor without ascribing a cell of origin.

Although the clinicopathologic features of NCS have been widely described, this tumor continues to be a problem for clinicians unfamiliar with its biological characteristics. The natural history of NCS remains to be defined. Currently, these tumors are considered to be aggressive with a variable prognosis.[50] They are difficult to treat effectively and few guidelines for their treatment have been reported.[46,50,55,60,65]

This study was designed to examine the clinical and pathologic differential diagnostic criteria and biological behavior of NCS. Five additional cases of this tumor are described in conjunction with an extensive review of the literature. This review addresses further the clinical presentation, behavior, and response to therapy of this neoplasm.

Methods

Five cases of NCS have been seen at the University of Florida's Shands Teaching Hospital (STH) and the Gainesville VA Medical Center (GVAMC) since 1982. Three were seen as a primary lesion, whereas the remaining two were referred to the Department of Surgery for further treatment. All charts were reviewed and the clinical data verified.

Tissue was fixed in 10% neutral buffered formalin and processed for routine histologic evaluation. Tissue was processed by standard procedures for ultrastructural analysis. Formalin-fixed, 5-μm paraffin sections of tumor and appropriate controls were used for immunoperoxidase staining. The avidin-biotin staining method

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of Hsu[66] was used in conjunction with antibodies to neuron-specific enolase (NSE), epithelial membrane antigen (EMA), cytokeratin (CK), and neurofilaments (NF) for staining of representative sections from each tumor.

Results

Case 1

A 52-year-old white man presented to the GVAMC with a 2-month history of a firm, painful, mass in the axillary tail of the left breast. Currettings were interpreted as consistent with infiltrating ductal carcinoma. One month later, he had a radical left mastectomy for two discrete 2.5-cm tumor nodules and an excisional biopsy of a contralateral, subcutaneous parasternal mass. Histologic and ultrastructural studies were consistent with NCS. In 2 months, regional and distant nodal metastases were observed. Multiple nodal, cerebral, and cutaneous lesions, but no lung lesions, were noted on CT scan at 3 months. He received palliative whole brain radiation therapy (3000 rads) and three courses of chemotherapy consisting of cyclophosphamide (1000 mg/m^2), doxorubicin (50 mg/m^2), and vincristine (2 mg). Initial tumor regression followed, with subcutaneous and cerebral recurrence occurring at 10 months. The patient died with tumor 12 months after his initial presentation.

Case 2

A 70-year-old white man with a 3-year history of well-differentiated lymphoma treated with cyclophosphamide and prednisone presented to STH with a 6-month history of a 3.5-cm firm, cutaneous nodule of the left thigh. The nodule was excised and interpreted as an "undifferentiated malignant neoplasm." Two months later he was diagnosed as having recurrent lymphoma and began a 28-month course of chemotherapy consisting of prednisone (80 mg) and chlorambucil (50 mg). At 17 months he had a 1.5-cm subcutaneous nodule on the left thigh, which was excised and interpreted as being consistent with NCS; wide local excision of the thigh lesion was performed with no residual tumor noted. The patient is currently alive at 36 months with no evidence of disease (NED).

Case 3

A 62-year-old white woman presented to a local physician with a subcutaneous lesion of unknown duration on the left buttock that had been incised and drained. The lesion enlarged and was excised at 4 months, with pathologic characteristics consistent with NCS. At 5 months she was observed to have left inguinal adenopathy, as well as recurrence at the previous excision site. At 6 months she was referred to STH for treatment, and a superficial inguinal node dissection and a wide excision of the original recurrent buttock lesion were completed. NCS was identified in specimens from both sites. She was subsequently treated with radiation therapy to both the inguinal areas (5000 and 6000 rads to the medial and left inguinal regions, respectively) and to the buttock (1000 rads). She is currently alive at 17 months and remains NED.

Case 4

A 67-year-old white man presented to a local physician with an 8-mm subcutaneous nodule of the forehead of 10 months' duration. The findings of an excisional biopsy were interpreted as NCS. Four months later he underwent a superficial right parotidectomy for metastatic tumor. He was subsequently treated at a second hospital with three courses of chemotherapy consisting of cyclophosphamide (750 mg/m^2), CCNU (70 mg/m^2), and methotrexate (15 mg/m^2), with subsequent subjective response. At 9 months he was observed at GVAMC to have an 8.0-cm right neck mass and cervical adenopathy. At 11 months, right parotidectomy and a conservative right neck dissection were completed. Tumor was found in 12 of 20 nodes, in extranodal tissue, and at the margin of resection in several sites. Radiation therapy was given to both the surgical bed (2000 rads) and to the ipsilateral neck (6000 rads). CT-guided biopsies demonstrated abdominal metastatic lesions at 19 months. Chemotherapy consisting of cyclophosphamide (1000 mg/m^2), doxorubicin (45 mg/m^2), and VP-16 (50 mg/m^2) was begun, but the patient was lost to follow-up after one course. He was readmitted to GVAMC at 26 months with a recurrent abdominal mass and restarted on the previous chemotherapy regimen with marked shrinkage in the tumor mass. He is currently alive at 28 months with no clinical evidence of tumor.

Case 5

An 82-year-old white man presented to STH with a 2-cm, rapidly enlarging, subcutaneous gluteal mass of 5 months' duration. The findings of the initial biopsy were interpreted as an "unusual primary carcinoma consistent with Merkel cell carcinoma." The tumor was widely excised at 1 month and diagnosed as NCS. At 8 months, regional adenopathy developed and the patient underwent a right superficial inguinal node dissection. Metastatic tumor was found in 5 of 11 nodes as well as in an extranodal soft tissue. No further treatment was initiated at that time. Eighteen months after presentation, lytic lesions of the T7 vertebrae were apparent, for which he received 3000 rads of local radiation therapy. He is currently alive at 27 months with metastatic disease.

Our five patients had a characteristic presentation of NCS. They were elderly patients, ranging from 52 to 82 years of age, who had a history of a slowly enlarging, firm skin nodule. The tumors ranged from 0.8 cm to 3 cm in maximal dimension, and were located on the lower extremities in three cases, and one each on the chest and the face. Results of the initial histologic interpretation of these lesions demonstrate the necessity of using additional diagnostic techniques. The initial lesion in two cases was misinterpreted; with the correct diagnosis of NCS being made on subsequent review. Contributory is the fact that NCS has a spectrum of histologic appearances that range from lymphomas, invasive carcinoma, and other small round cell tumors. In general, NCS was noted to be a monomorphic, nonorganoid, small round cell tumor arising in the dermis (Fig. 1). Electron microscopic studies demonstrated the presence of electron-dense, neurosecretory type granules in the cytoplasm and cell processes, as well as collections of intermediate filaments and immature cell junctions (Fig. 2). Immunoperoxidase staining for NSE, EMA, and cytokeratins demonstrated both intra- and intertumor variations. NSE was consistently demonstrated, whereas staining of paraffin sections for NF was very inconsistent.

The clinical behavior of NCS in these five patients was consistent with that of a biologically aggressive tumor. Local recurrence was observed in four patients (cases

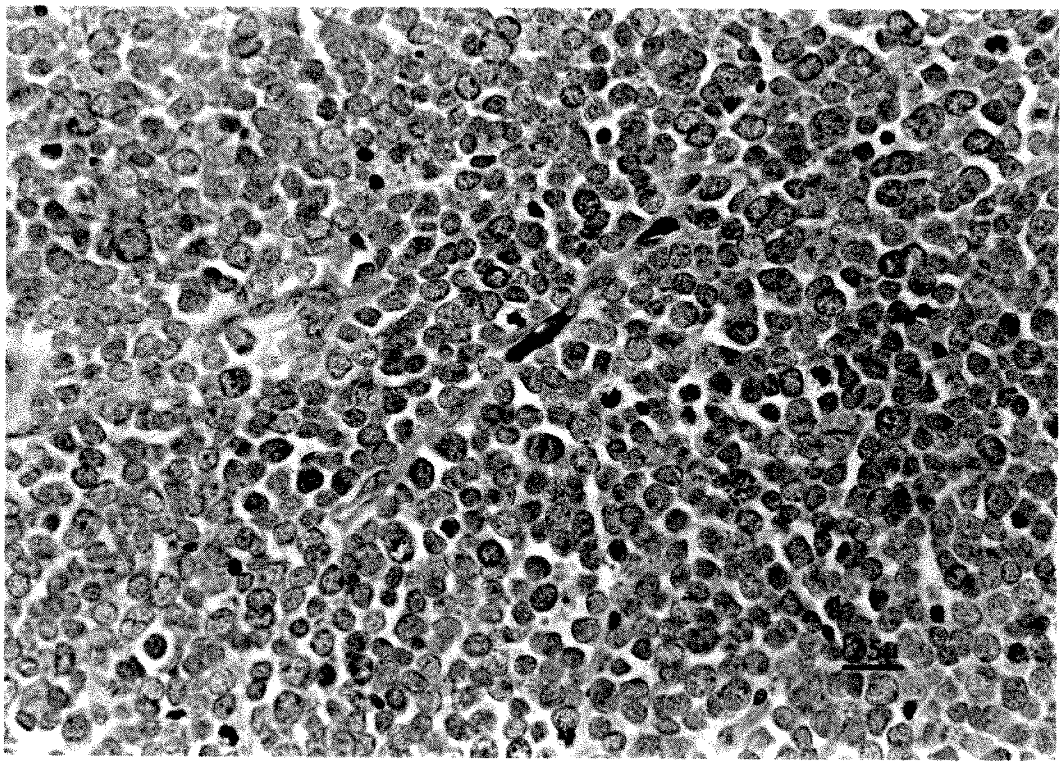

FIG. 1. Pathologic features of neuroendocrine carcinoma of the skin. Hematoxylin and eosin stain of sheets of monomorphic tumor cells (original magnification ×250).

1–4) with an average of 6 months (range: 1–17 months) from the time of presentation. Regional nodal metastases developed in case 5 without prior local recurrence, whereas cases 1, 3 and 4 progressed to regional nodal involvement 1–9 months after diagnosis. Distant metastasis occurred in three of the four patients (cases 1, 4,

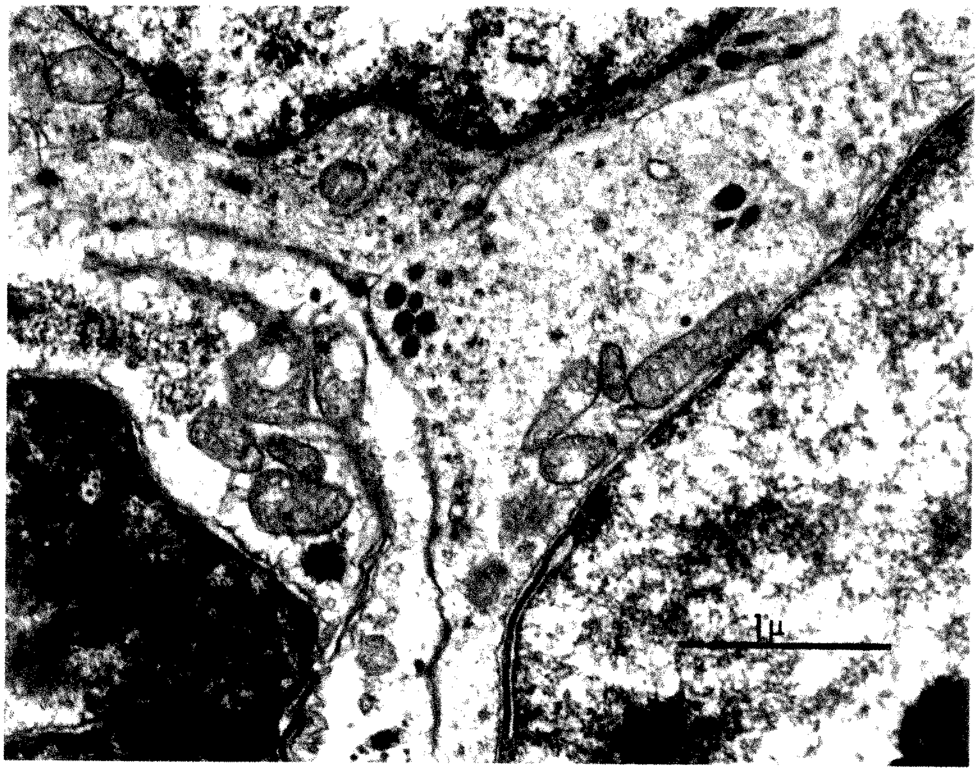

FIG. 2. Ultrastructural features of neuroendocrine carcinoma of the skin (×28,000). Note the presence of neurosecretory-type electron-dense granules and primitive intercellular junctions.

TABLE 1. *Clinical Features of Neuroendocrine Carcinoma of the Skin at Presentation*

Age (years)	
Range (N = 332)	15–97
Mean (N = 269)	68.2
Sex (N = 316)	
Male	48.1%
Female	51.9%
Primary lesion site (N = 315)	
Head and Neck	48.9%
Upper Extremities	15.6%
Lower Extremities	30.2%
Trunk	3.8%
Multiple	1.5%

and 5) with nodal involvement 3–19 months (mean: 13.3 months) after initial presentation. Only case 1 has died of tumor.

Discussion

Neuroendocrine carcinoma of the skin is an infrequent, but by no means rare, primary cutaneous neoplasm. To date, the natural history of NCS remains undefined. The reason for this deficiency is best explained by the fact that previous studies have focused on the pathologic rather than the clinical and/or the biological features of the tumor. The elucidation of these features will aid pathologists and clinicians to initiate both a prompt diagnosis and effective therapy. We have added five additional cases to the over 400 cases of NCS reported in the literature,[1-65] and have undertaken a comprehensive review of the reported cases. Our purpose is to better comprehend NCS's biological behavior, to delineate its essential diagnostic features, and to propose guidelines for its treatment.

TABLE 2. *Clinical Behavior of Neuroendocrine Carcinoma of Skin*

	No. of Patients (%)
Local recurrence	
Patients with ≥6 months F/U*	80/220 (40.0)
Multiple 30/88 (34.1%) (range 2–9×)	
Time from initial diagnosis to first local recurrence: 1–54 months (mean: 10.1 months)	
Regional lymph node metastasis	
All patients	
At presentation	31/254 (12.2)
Following initial diagnosis	86/187 (46.0)
Patients with ≥12 months F/U	107/193 (55.4)
Time from initial diagnosis to nodal metastasis: 1–202 months (mean: 13.4 months)	
Distant metastasis	
All patients	82/226 (36.3)
Multiple sites	10/82 (12.2)
Patients with ≥24 months F/U	73/148 (49.3)
Time from initial diagnosis to distant metastasis: 11 days to 96 months (mean: 18.3 months F/U)	

F/U = follow-up.

NCS is primarily a lesion of sun-exposed skin of the elderly (Table 1). Essentially 50% of reported NCS lesions are located on the head and neck, whereas less than 5% involve the skin of the trunk. Patient age is reported to vary from 15 to 97 years with a mean of 67.9 years. There is no apparent sexual predominance as has been reported previously.[23,25,32,41,50,59,60,65] Patients often have a history of a slowly enlarging, pink to violaceous plaque or nodular subcutaneous lesion that suddenly rapidly increases in size.

NCS behaves as an aggressive tumor with local recurrence and metastases as common features (Table 2). Forty per cent of the patients who were followed a minimum of 6 months or who died before this time, exhibited local recurrence, with close to one third having multiple recurrences. The mean time from diagnosis to first local recurrence was 10.1 months in 220 cases (range: 1–54 months). Approximately 75% (53 of 71) of reviewed cases with local recurrence and 6 months or more follow-up exhibited disease progression with regional nodal and/or distant metastasis. Of these 53 patients, 29 (55%) died of tumor, whereas 30% were alive at the time of publication (Table 3).

NCS has a propensity for early involvement of regional lymphatics (Table 2). Regional nodal metastases were evident in 55% of the reported patients who were followed for 12 months or more, or who died before this time. Adenopathy was noted from 1 to 202 months (mean: 13.4 months) after initial diagnosis. Nodal involvement at the time of initial presentation was observed for 31 of 254 patients (12.2%). A total of 37 of 74 (50%) patients with regional nodal metastasis subsequently developed distant metastases, of which 27 (73%) died of the disease. Only six of 74 (16.2%) reported patients have died of tumor without further metastatic disease developing (Table 3).

Distant metastases occurred in 82 of 226 (36.3%) reported cases of NCS; 10 of 82 (12.2%) exhibited multiple metastases (Table 2). Of the 148 patients with a reported follow-up of 24 months or greater, or who died before this interval, 73 (49.3%) had distant metastatic disease. The mean time from initial diagnosis to discovery of metastatic tumor was 18.3 months (range: 11 days to 96 months). Sites for distant metastatic disease in order of decreasing frequency include: lymphatics, liver, bone (including vertebrae, as in case 5), brain (as in case 1), lung, and skin. Retroperitoneal lymph nodes (as in case 1) are the most common site for distant nodal spread. Involvement of the parotid gland (as in case 4) is consid-

TABLE 3. *Patient Follow-up Status for Local, Regional, and Distant Metastases*

	No. of Patients	Patient Status				
		LTFU	Alive	AWT	DOC	DOD
Local recurrence ≥6 months F/U						
No further lesions	18 (25.3%)	3 (16.6%)	12 (66.7%)	—	2 (11.1%)	1 (5.3%)
Local LN Mets only	19 (26.8%)	3 (15.8%)	8 (42.1%)	—	5 (26.3%)	3 (15.8%)
Local LN/Dist Mets	23 (32.4%)	0	5 (21.7%)	1 (4.3%)	0	17 (73.9%)
Distant Mets only	11 (15.5%)	1 (9.1%)	2 (8.2%)	—	0	8 (72.7%)
Total	71 (100%)	7 (9.9%)	27 (38.0%)	1 (1.4%)	7 (9.9%)	29 (40.8%)
Regional LN metastasis ≥12 months F/U						
No Further Mets	37 (50%)	2 (5.4%)	21 (56.8%)	0	8 (21.6%)	6 (16.2%)
Subsequent Dist Mets	37 (50%)	3 (8.1%)	5 (13.5%)	2 (5.4%)	0	27 (73.0%)
Total	74 (100%)	5 (6.8%)	26 (35.1%)	2 (2.7%)	8 (10.8%)	33 (44.6%)
Distant metastasis ≥24 months F/U						
Literature 1*	64	4 (6.3%)	10 (15.6%)	6 (9.4%)	1 (1.5%)	43 (67.2%)
Literature 2†	77	—	20 (26.0%)	—	—	57 (74.0%)

* Literature 1: excludes patients reported by Silva et al.[50]

† Literature 2: excludes 18 patients reported by Silva et al.[50] and excludes LTFU, and DOC patients and alive includes AWT patients.

LTFU = lost to follow-up; AWT = alive with tumor; DOC = dead from other causes than tumor; DOD = dead of disease; F/U = follow-up; LN = lymph node; Mets = metastasis.

ered to be by direct extension rather than by metastasis.[60]

Death from tumor has been reported to vary from 67% to 74% (Table 3) for patients with distant metastases. For 45 patients in whom precise clinical information was available, death from tumor occurred within an average of 6.2 months from diagnosis of widespread metastatic disease.

The overall prognosis for patients with NCS has been reported to vary. A Kaplan-Meier survival analysis of cases, both those reported and including our five cases, is seen in Figure 3. Overall survival rates are: 1-year, 88%; 2-year, 72%; and approximately 55% at 3 years. The lack of sufficient numbers of patients with 3 or more years of follow-up precludes accurate determination of survival. There was no significant correlation between survival and patient age. Female survival was significantly greater ($p = 0.0069$ Wilcoxon) than that for males. Two-year and 3-year survival rates for males and females were, respectively, 58% *versus* 79.4% and 35.6% *versus* 67.6%.

The metastatic potential of NCS mandates that an early and accurate diagnosis be made by the clinician and the pathologist. The majority of these lesions arise in the dermis and extend into the subcutaneous fat. The spectrum of histology of NCS can make a definitive diagnosis difficult. Goepfert et al.[46] reported that misdiagnosis was as great as 66% when light microscopy was used alone. The differential diagnosis for NCS includes: metastatic oat cell carcinoma, lymphoma, amelanotic melanoma, and adnexal tumors. The correct diagnosis is best derived from a combination of a thorough clinical evaluation, coupled with light and electron microscopy with a defined panel of immunoperoxidase stains. Three principle ultrastructural features aid in differentiating NCS from these other tumors: 75–200-nm electron-dense neurosecretory type granules, paranuclear bundles of intermediate filaments (fibrous bundles),[60] and primitive (nondesmosomal) junctional complexes (Fig. 2). These features are not associated with other primary cutaneous tumors. Immunoperoxidase staining for NSE, EMA, and cytokeratins is highly recommended. Monoclonal antibody to the leukocyte common antigen (LCA) can be used on paraffin sections to rule out a diagnosis of lymphoma.

Treatment guidelines are designed and implemented after thorough clinical evaluation and regular follow-up. The following guidelines for the clinical management of

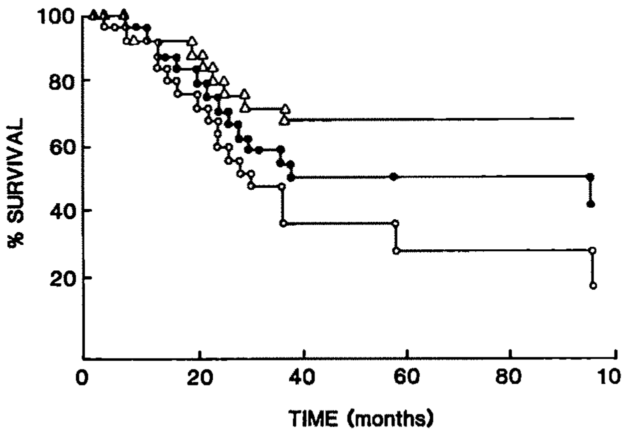

FIG. 3. Kaplan-Meier survival analysis of 172 patients with neuroendocrine carcinoma of the skin. Females have a significantly greater ($p < 0.007$) survival at 24 and 36 months compared with males.

NCS are based on our experiences as well as those of others reported in the literature.

Among reported cases, surgical treatment for primary NCS has varied from incision and drainage to wide excision. Local recurrences arise primarily from an inadequate excision of the primary tumor (the tumor approximates or contaminates the margins of resection). Reported tumors vary from 4 mm to 12 cm, with two thirds being 2 cm or less in greatest dimension. Thus, the majority of the lesions are amenable to excision. We and others[41,46,50,60,65] recommend a wide excision (2-3-cm margin) of the primary lesion be performed with similar techniques implemented for squamous cell carcinoma of the skin.

Prophylactic nodal dissection has not been completed on a routine basis. Silva et al.[50] recommended nodal dissection be performed if the primary tumor was 2 cm or greater, if there is a high mitotic rate (10 HPF), or if the hyperchromatic cell pattern predominates. Relative to head and neck lesions, these authors recommend nodal dissection be performed when the primary tumor is situated in proximity to the nodal regions.[46] We concur that a therapeutic regional nodal dissection be performed for adenopathy as well as for the presence of vascular invasion. In addition, all patients with a primary tumor of the head and neck should undergo radical neck dissection as Goepfert et al.[46] have reported a 75% failure rate for untreated nodes. Patients with midline head and neck primary tumors should undergo bilateral radical neck dissection, which may be staged. Should prophylactic regional node dissection not be initiated, careful patient education and interval physician examination are prudent.

NCS is a radiosensitive tumor.[50,65] Irradiation has been used prophylactically as well as for recurrent and metastatic lesions. Silva and co-workers[46,50] consider that radiation therapy failures are "geographic misses" due to inadequate field margins. They recommend prophylactic radiation therapy be used to reduce local recurrence and/or metastasis. We recommend that radiation therapy be completed in the following cases: (1) where the tumor approximates the margin of resection, (2) when there is histologic evidence of vascular space involvement, and/or (3) if nodal metastasis is present. In these clinical settings, radiation portals should include the tumor bed and the lymphatics in transit. Silva et al.[50] have reported no radiation therapy failures for doses ≥ 4500 rads delivered over 5 weeks. Until a dose-response curve is available for NCS, we believe that equivalent irradiation dosage should be administered.

Chemotherapy has been used in the treatment of NCS where there has been an absence of local tumor control. To date, a wide variety of cytotoxic agents have been used and include: VP-16, cisplatin, CCNU, methotrexate, vincristine, doxorubicin, and cyclophosphamide. These regimens have been applied with variable objective response being reported. Kroll and Toker[20] note that tumor regression with chemotherapy was rapid but that recurrence occurred within 6–12 months. Other studies have reported similar results.[50,55,60] The infrequent incidence of the tumor precludes a prospective study for determination of the superior drug regimen. We are currently using cyclophosphamide, doxorubicin, and VP-16 to treat systemic disease in one of our patients (case 4). We and others[50] recommend that the same regimen used for the treatment of oat cell carcinoma should be considered for the treatment of systemic NCS.

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Lymphoid Subpopulation Changes after Thermal Injury and Thermal Injury with Infection in an Experimental Model

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Subpopulation analysis of peripheral blood lymphocytes is a frequently used measure of immunocompetence. Yet, little is known about the lymphocyte subpopulations in the circulation and lymphoid organs after severe trauma. Blood, spleen, and lymph node (LN) subpopulations were compared in a rat model of burn injury (B) and burn injury with infection (BI). B and BI rats received 30% total body surface scald burns. Infection was induced by seeding wounds with *Pseudomonas aeruginosa.* Subpopulations were identified by flow cytometry 48 hours after burn. Helper lymphocytes were selectively depleted from the circulation of BI but not B animals, which caused the ratio of helper to suppressor cells (HSR) in BI animals to decrease significantly compared with the unburned controls. Both LN helper and suppressor cells were decreased in BI animals and the HSR was unchanged, but a selective reduction in suppressor cells in B LN increased the HSR relative to unburned controls. Spleen subpopulations were unchanged for both B and BI groups. Subpopulation changes after trauma and infection were different for each tissue examined.

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INFECTION STILL ACCOUNTS for a large fraction of the mortality observed in patients with large burns.[1,2] The susceptibility of burned patients to infection by organisms that are ordinarily nonpathogenic suggests an acquired defect in host defense mechanisms. Many aspects of host defense have been examined in an attempt to define this underlying defect, and many cellular and humoral aspects of host defense have been found to be abnormal.[3-8] However, none of the abnormalities described can be pinpointed as the cause of the observed increased susceptibility to infection.

Several conditions that present clinically with increased risk of infection are accompanied by relative changes in lymphocyte subpopulations,[9] usually described as a decrease in the ratio of T-helper to T-suppressor cells (HSR) in the circulation. The shift in this ratio may reflect a change in the balance between immune stimulation and suppression. An inappropriate change in this regulatory balance could lead to decreased resistance to infection.

Lymphocyte subpopulation changes are usually measured in lymphocyte samples from peripheral blood. Peripheral blood lymphocytes are a relatively small fraction of the total lymphocyte pool and may not present a valid picture of the immunological state of the individual. This mobile pool of cells might be expected to fluctuate more widely in response to stress or infection than the lymphocyte populations in the relatively immobile lymphoid tissues. Additionally, the accuracy of measurements of peripheral blood lymphoid cells can be impaired by atypical leukocyte populations, which are often found in the circulation of trauma victims several days after severe injury.[10] Sampling of a greater range of lymphocyte sources, such as spleen and lymph nodes, may give a more general picture of immunocompetence than assessment of peripheral blood alone.

We have analyzed the changes in lymphoid cell populations that occur after either burn injury or burn injury complicated with infection in a well-defined burn and burn-infection model.[11] The results show that relative increases in the proportion of suppressor lymphocytes relative to helper lymphocytes (decreases in the HSR) do

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

In conducting the research described in this paper, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Research Council.

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not occur in the blood, spleen, or lymph nodes of infection-susceptible but uninfected burned animals. Decreased HSR was observed only in the blood of burned animals with infection.

Methods

Male albino Sprague-Dawley rats (300–400 g) were randomly assigned to one of three groups: an unburned control group, a burned group, or a burned group with infection. All rats were anesthetized with pentobarbital (IP, 1 mg/100 g body weight), and those in the burned groups were shaved, placed in a plastic mold that defined the burn surface area, and subjected to a 30% total body surface full-thickness burn by 10-second immersion in boiling water.[11] Infection was induced by placing 1 ml of a 16-hour broth culture containing approximately 10^8 *Pseudomonas aeruginosa* (strain 59-1244) on the burn wound within 1 hour of scalding.[12] At sacrifice, 48 hours after infection, the rats were anesthetized with pentobarbital and exsanguinated by opening the body cavity and bleeding from the hepatic vein. Subsequently, blood, spleen, and mesenteric lymph nodes were taken for cell analysis.

Peripheral blood leukocyte counts were made using a Coulter Counter (model ZM, Coulter Electronics, Hialeah, FL), and differential analyses were performed on blood smears. Spleen cells were obtained by disrupting the spleen and passing the cell suspension through a loosely packed cotton wool column to remove debris. The lymphoid cells from blood and spleen were separated from other cells by centrifugation over a Ficoll-Hypaque density gradient.

Lymph nodes were trimmed of excess tissue and minced with scissors over a 60-mesh stainless steel screen. The cells passing through the screen were passed through a loosely packed cotton wool column to screen out extraneous pieces of tissue. More than 95% of the lymph node cells obtained in this manner were lymphocytes and these cells were used without further purification. The isolated cells from each tissue were washed and samples of the cells were used to prepare slides for differential analysis. The remaining cells were stained with appropriate lymphocyte mouse monoclonal reagents obtained from Pel-Freez (Roger, AZ). The monoclonal reagents attached to the cell surface were further bound with affinity-purified, fluorescein-labeled goat anti-mouse IgG (Fab2′ fragments) as a second step reagent.

The fluorescently stained cells were then analyzed, using a Fluorescence Activated Cell Sorter, model 400 (Becton Dickinson, Mountain View, CA), modified by addition of a 90-degree light scatter PMT and a consort 40 data analysis system. For each sample, 5000 cells were analyzed and the numbers of cells fluorescently stained with T lymphocyte (W3/13), suppressor/cytotoxic (OX-8), or helper/inducer (W3/25) reagent were determined. A negative control using a monoclonal antibody to human T cells (which had no specificity for rat cells) was run with each cell preparation to determine an appropriate cutoff to distinguish negative from positive cells. The positive cutoff was set at a point defining the upper 2% or less of the background control and the number of background control cells beyond the cutoff was subtracted from each sample. Contamination by nonlymphoid cells was monitored by analyzing forward and 90-degree scattered light. Those cells with light scatter intensity not typical of normal lymphocytes were not analyzed (gated).

The proportion of the positive cells for each of the subsets were compared among the three animal groups. Statistical analysis consisted of a pairwise analysis of means (t-test) with a Bonnferroni adjustment, performed on a VAX 11/780 (Digital Equipment Corporation, Maynard, MA) using program P7D (BMDP Statistical Software, Los Angeles, CA).

Results

Light scatter analyses of cells from each tissue were compared with morphologic analyses of cells on Wright's stained preparations to determine the effectiveness of the light scatter analysis as a measure of nonlymphoid cell contamination. Ficoll-Hypaque purified blood cells from burned animals showed no significant change in either light scatter characteristics or Wright's stain morphologic characteristics when compared with unburned controls (Table 1). Blood cells from burned animals with infection, however, showed a significant decrease in the proportion of cells ($p < 0.01$) with scatter characteristics typical of normal lymphocytes. This decrease correlated with a decrease in the proportion of cells with lymphocyte morphologic characteristics and an increase in the proportion of cells with morphologic characteristics of immature granulocytes or atypical mononuclear cells. There was no significant change from control in the light scatter characteristics or cellular morphologic characteristics of lymph node or spleen cells from burned or burned animals with infection.

Surface antigen analysis was performed on blood mononuclear cells that exhibited light scatter typical of normal lymphocytes (Fig. 1). The proportion of helper lymphocytes was decreased, whereas suppressor/cytotoxic lymphocytes were increased in the blood of burned rats with infection relative to control, but not in the blood of animals subjected to burn alone. This relative shift in subpopulations caused the HSR of circulating lymphocytes to decrease significantly ($p < 0.01$) in burned animals with infection compared with controls. Lymph node cells from burned animals with infection (Fig. 2) consisted of a significantly smaller proportion of T-lymphocytes (Pan-T) than uninfected animals as well

TABLE 1. *Differential Analysis of Ficoll-Hypaque Preparations by Light Scatter and Wright's Stain Morphology**

Cell Source/Group	Cells ± SD (% in "Lymphocyte" Gate)	Significance Level	% Lymphocytes (Wright's Stain)
Blood			
Control	77.6 ± 11.01	ns	91.0 ± 9.9
Burned	73.8 ± 8.8	ns	87.0 ± 11.4
Burned-infected	56.4 ± 16.3	(vs. control $p < 0.01$)	74.9 ± 16.4
Spleen			
Control	66.2 ± 12.0	ns	99.5 ± 1.0
Burned	69.2 ± 13.3	ns	98.7 ± 1.8
Burned-infected	61.3 ± 18.7	ns	95.8 ± 11.4
Lymph node			
Control	91.8 ± 4.9	ns	100 ± 0
Burned	89.9 ± 7.5	ns	99.9 ± 0.1
Burned-infected	92.0 ± 8.1	ns	99.8 ± 0.5

* Cells were analyzed for light scatter characteristics by flow cytometry and the number of cells falling within the lymphocyte "window" determined. A small aliquot containing approximately 10^5 cells was used to make a cytocentrifuge slide that was stained using Wright's stain and examined for the relative number of lymphoid and nonlymphoid cells under light microscopy.

as reduced proportions of both helper and suppressor lymphocytes. In burned uninfected animals the proportion of suppressor lymphocytes was lower than that of control animals, but the proportion of helper and Pan-T positive cells was not significantly different. Spleen cells from infected animals contained a small subpopulation of cells (5–10% of the total) that bound monoclonal antibody control reagents. Control reagents had the same mouse immunoglobulin isotype as the monoclonal reagents, but had no reactivity to rat cells. Therefore, the data depicted for spleen cells (Fig. 3) from infected animals may overestimate the true value for one or more of these populations by 5–10%. However, there was no significant difference in any of the three T-lymphocyte subpopulations or the HSR in the spleens of burned or burned animals with infection compared with unburned controls.

A summary of the HSR determined for each tissue is depicted in Figure 4. Infected animals show more variation in the ratio than the other groups, having a decreased ratio in blood but an increased (although statistically not significant) ratio in lymph node. The HSR increased in the lymph node even though both helper and suppressor/cytotoxic subsets decreased, because there was a disproportionate decrease in suppressor cells. The decrease in suppressor cells present in the lymph nodes of burned animals caused an increase in the HSR. This was the only difference in any of the lymphocyte subpopulations induced by the burn injury alone. The HSR determined in spleen cells was not significantly different from control in either of the experi-

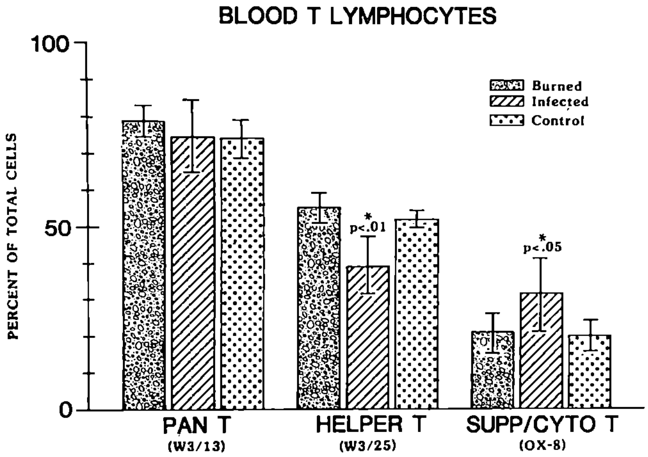

FIG. 1. The proportion of Ficoll-Hypaque purified blood cells positive for three T-lymphocyte surface antigens. Cells from burned and burned-infected and control rats were analyzed by flow cytometry for each of the three major T-lymphocyte surface antigens. The number of cells staining positively for each antigen is expressed as the mean percentage of total cells analyzed ± SD (N = 10).

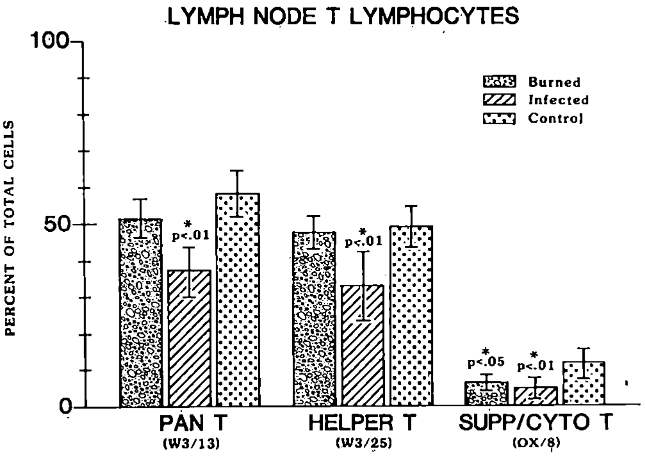

FIG. 2. The proportion of lymph node cells positive for the T-lymphocyte surface antigens. Conditions are the same as for Figure 1.

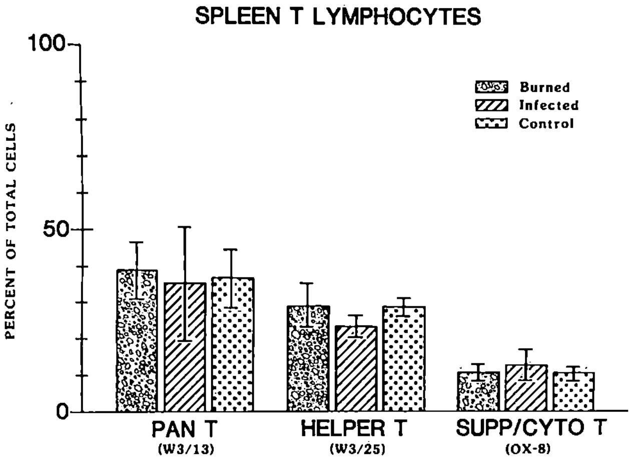

FIG. 3. The proportion of Ficoll-Hypaque purified spleen cells positive for the T-lymphocyte surface antigens. Conditions are the same as for Figure 1.

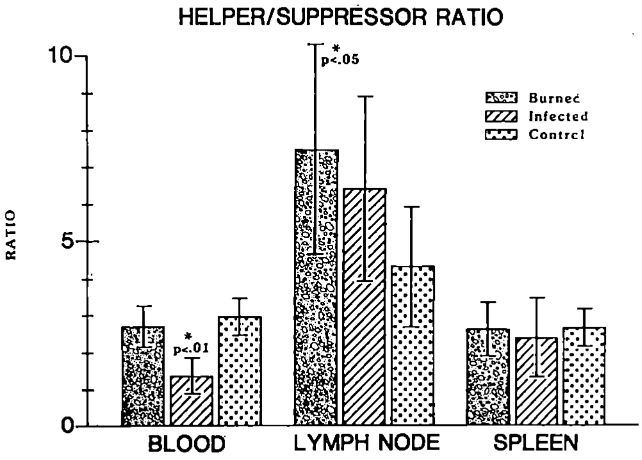

FIG. 4. The ratio of T-helper to T-suppressor/cytotoxic lymphocytes from blood, spleen, and lymph node for control, burned, and burned-infected rats. Conditions are the same as for Figure 1.

mental groups even though the number of lymphoid cells in the spleen was decreased sharply in the infected animals (data not shown).

The changes induced by burn injury alone and burn injury with infection are summarized in Table 2. A decrease in the suppressor subpopulation in the lymph nodes was the only significant subpopulation change for the infection-susceptible, but uninfected, burned animals. In the infected animals, proportional decreases were observed in all lymph node T cell subpopulations. In the blood of infected animals, the proportion of helper lymphocytes decreased, whereas the proportion of suppressor lymphocytes increased. The only changes in HSR were a decrease in the blood of infected animals and an increase in the lymph node of burned animals without infection.

Discussion

Other studies have been interpreted as showing that burn injury increases the relative proportion of suppressor cells (decreases HSR) in the burned host. It has been implied that such a shift in subpopulations decreases the capacity of the host to mount an immune response and thereby decreases resistance to infection. It is important to note that the changes in HSR are relative and that an absolute increase in the number of suppressor cells has not been reported. Using a mouse model, Zapata-Sirvent and Hansbrough[13] found a decreased spleen cell HSR to be correlated with decreased skin hypersensitivity to dinitrofluorobenzene 10–14 days after thermal injury. In a later study[14] Zapata-Sirvent et al. described a correlation between decreased hypersensitivity and mortality after infection induced by cecal ligation and puncture. In a rat burn infection model we have found that a decrease in the HSR in peripheral blood occurred only in the presence of infection and not as a consequence of injury *per se.*[15] In human burn patients a correlation between a decreased HSR and increased susceptibility to infections has been reported in patients with large burns by McIrvine et al. and Antonacci et al.[8,16] They reported decreased HSR in patients with burns covering more than 30% of the total body surface. In one study,[8] decreased helper/suppressor ratios occurring more than 14 days after burn were positively correlated with the occurrence of fatal sepsis. As in most clinical studies it is difficult to determine whether lymphocyte subpopulation changes are related to the cause of infection or are an effect of infection.

In the current study, the blood HSR measured 48 hours after injury and infection was decreased in infected animals. In uninfected burned animals, however, the HSR was not significantly different from control. Since infected animals have decreased circulating lymphocytes,[15] the change in proportion of helper and sup-

TABLE 2. *Comparison of Lymphocyte Subpopulations and HSR from Blood, Lymph Node, and Spleen**

Tissue	Group	Pan T	Helper	Suppressor	H/S Ratio
Blood	Burned	ns	ns	ns	ns
Blood	Infected	ns	−32.3‡	+19.2†	−53.7‡
Lymph node	Burned	ns	ns	−43.8†	+72.1†
Lymph node	Infected	−36.2‡	−32.9‡	−56.9‡	ns
Spleen	Burned	ns	ns	ns	ns
Spleen	Infected	ns	ns	ns	ns

* Values shown are percentage changes from the unburned control.
† Significant at 0.05 level.
‡ Significant at 0.01 level.
ns = change not statistically significant.

pressor cells due to infection was related to depletion of helper cells from the circulation, rather than any increase in suppressor cells. The observed decrease in blood HSR appears after rather than before infection. Susceptibility to infection after injury cannot be attributed to any relative increase in the number of suppressor/cytotoxic cells in the blood.

There was no decrease in the HSR in the mesenteric lymph nodes or spleens of the infected animals (Table 2) as was observed in blood. The total number of lymphocytes in the lymph nodes and spleen is much greater than in peripheral blood. The changes seen in blood subpopulations may represent transient depletion of selected subsets of lymphocytes as they migrate from the peripheral circulation. The subsets of the lymphocytes in the circulation are apparently subject to wider fluctuations in response to infection than those that occur in the total lymphoid population. The lack of uniformity among subpopulation shifts in the different tissues demonstrates that each of the lymphoid tissues acts, to some extent, as an individual compartment rather than as part of a common reservoir of lymphoid cells.

Although relative changes in lymphocyte subpopulations do not appear to accompany the increased susceptibility to infection after burn injury, subpopulation analysis of peripheral blood may have clinical use as an indicator of existent sepsis, since HSR appears sensitive to the presence of infection. That possibility awaits further study. Since the immune response results from a complex interaction among several subpopulations of cells, measurement of cell function rather than simple enumeration of subpopulations is more likely to yield information about the nature of the defects in host defense after burn injury.

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Congenital Angiodysplasia of the Superficial Venous System of the Lower Extremities in Children

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Congenital angiodysplasia of the superficial venous system (SVS) of the lower extremities was diagnosed in 24 children 3–15 years of age. Nine patients presented with painful swelling in the affected limb. Venectasia and spongy venous masses were the main morphologic changes in the current series. Selective ascending functional phlebography and superficial phlebography were used to assess the anatomic extension of the lesions and to evaluate the functional status of the involved extremity: 14 patients had only SVS angiodysplasia, in 10 patients additional pathologic features of the deep veins (DV) were found. Venous reflux was demonstrated in 16 patients and significant venous insufficiency was detected in five patients. The patients were classified into three groups according to the severity of the disease: mild (11 patients), moderate (8 patients), and severe (5 patients). The prognostic and the long-term outcome of surgical treatment can be predicted by the depth and the extension of the angiodysplastic lesions.

CONGENITAL VASCULAR MALFORMATIONS of the lower extremities are relatively rare. The variability of their clinical and radiologic presentation may create some confusion in the diagnosis and raises controversy in the therapeutic approach. The prognostic outcome of these lesions is frequently unclear. Superficial proliferative vascular lesions with increased mytotic activity are defined as hemangioma.[1-3] Vascular lesions that grow with the child and show normal endothelial mytotic activity are called malformations. Venous malformations, venous angiodysplasia, were classified by Malan and Puglionisi,[4] and their radiologic features were clearly defined.[3,5,6]

The venous anomalies of the lower extremities are divided into two groups: (1) deep venous (DV) malformations involving the central veins, which are the main draining pathways of the lower extremity; and (2) superficial venous system (SVS) malformations involving the superficial venous pathways rather than the deep venous trunks.

This study presents our experience with congenital angiodysplasia of the SVS of the lower extremities in children. The therapy of these unusual lesions has been based on a diagnostic approach that delineates the morphologic changes and assesses the degree of venous dysfunction.

Materials and Methods

Eighty-five children 2–15 years of age with congenital and acquired vascular disorders of the lower extremities underwent a complete physical examination, including measurements of leg length and circumference in both the recumbent and standing positions.

The main vessels were examined by Doppler ultrasonography. The partial oxygen tension of the venous blood was determined to identify arteriovenous fistulas. Elongation or shortening of the involved limb and soft tissue changes such as phleboliths and hemangiomas were demonstrated by plain x-ray films.

The patients underwent selective ascending functional phlebography. The posterior tibial vascular bundle located behind the medial malleolus was exposed under local anesthesia, and the vein was cannulated. Hypaque 50% (1 ml/kg to a maximum of 20 ml) was rapidly injected without a tourniquet. Three radiographs of the lower extremity were obtained while the patient was standing and the leg was internally rotated: immediately after injection, 30–40 seconds later after active functional stress consisting of lifting the heel four times, and 3 minutes after the first radiograph. Normally, the contrast material is completely cleared from the venous system in 3 minutes. The degree of venous

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TABLE 1. *Clinical Findings in 24 Patients with SVS Angiodysplasia*

Signs and Symptoms	No. of Patients
Pain	9
Local swelling	5
Increased leg circumference	11
Decreased leg circumference	5
Port wine stain	9
Intracuticular venodilatation	7
Subcutaneous venodilatation	10
Spongy venous mass	12

insufficiency is determined by the amount and location of the contrast material remaining in the lower extremity on the last radiograph. In children younger than 3 years, phlebography was performed under general anesthesia in the recumbent position, and functional parameters could not be measured. Using selective ascending functional phlebography, we define three degrees of venous insufficiency: (1) first degree: retention of no more than 50% of the contrast material in either superficial or deep venous system, (2) second degree: retention of less than 50% in both systems simultaneously, and (3) third degree: retention of more than 50% of the contrast material in both venous systems.[7]

In addition, 12 patients underwent superficial phlebography. Hypaque 50% was injected rapidly by hand without a tourniquet into one of the subcutaneous veins of the foot. Radiographs were obtained with the patient at a 45-degree oblique position.

The severity of the disease was graded as the following: (1) mild, cosmetic defect; (2) moderate, cosmetic defect and local pain; and (3) severe, painful and swollen leg, muscle atrophy, hemarthrosis with significant disability.

TABLE 2. *Functional and Morphologic Phlebographic Findings in 14 Patients with SVS Angiodysplasia and Normal Deep Veins*

Phlebographic Findings	No. of Patients
Venous reflux	7
Typical communicants	2
Atypical short communicants (Fig. 2A)	5
Venous insufficiency	5
First degree	4
Second degree	1
Morphologic variations	14
Intramuscular thigh and knee joint angiodysplasia (Fig. 1)	5
Subcutaneous angiodysplasia	3
Ankle and foot angiodysplasia	2
Angiodysplastic formation of knee region	1
Extended subcutaneous and intramuscular lesion (thigh and leg)	1
Intramuscular leg angiodysplasia	1
Subcutaneous embryonal angiodysplastic trunk (Fig. 2B)	1

Twenty-three operations were performed in 18 patients (see Table 4).

Results

Congenital angiodysplasia of the superficial venous system was diagnosed in 24 children (15 girls and 9 boys). The age range was 3–15 years and the median age was 9 years. All patients had unilateral pathology (left, 14; right, 10).

Clinical Examination

The main clinical findings are summarized in Table 1. Nine patients had pain in the affected limb while standing or walking for 5–10 minutes. In most patients, the pain was localized to the lesion. In a few children, the pain extended distally from the lesion to the foot and was accompanied by remarkable swelling. There was no significant difference in length of the extremities. However, 11 patients showed an increase in circumference of the involved leg ranging from 2 to 7 cm. None of the patients had clinical or sonographic signs of arteriovenous malformations. Intracuticular lesions ranged from a typical "port wine stain" to bluish discoloration with some skin irregularity due to abnormal venous dilatation of the deeper layers of the skin.

The subcutaneous lesions consisted of either a single dilated vein or conglomeration of dilated and tortuous veins with or without spongy venous masses. Phleboliths were occasionally palpated in the collapsed spongy lesions. Subfascial angiodysplastic malformation should be suspected in patients where leg circumference decreases when measured in the upright *versus* recumbent position. This is due to the presence of collapsed angiodyspastic lesions and muscle atrophy.

Radiological Findings

Selective functional ascending phlebography and superficial phlebography were used to assess the anatomic and functional disorders in SVS angiodysplasia.

Based on these examinations, the patients were divided into two groups. In 14 children (group A), selective ascending functional phlebography demonstrated normal drainage *via* deep veins of the thigh and calf (Table 2), with either no reflux in half of them (Fig. 1A) or mild reflux in the rest (Fig. 2A). In five patients of this group, venous insufficiency of first or second degree was found. Superficial angiodysplastic lesions in these patients were demonstrated only by superficial phlebography. Lesions ranged from a persistent embryonal veins (Fig. 2B) to large, spongy malformations (Fig. 1B). In the other 10 patients (group B), abnormal deep venous system was demonstrated (Table 3); saccular an-

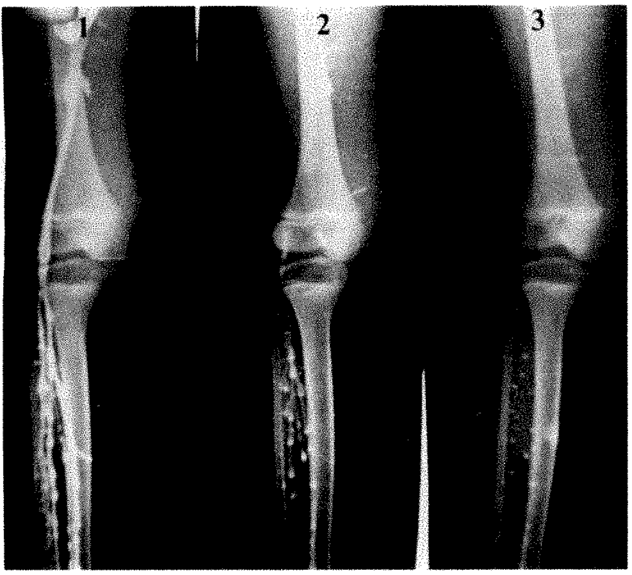

FIG. 1A. Selective ascending functional phlebography in a 9-year-old girl demonstrates normal deep veins of affected lower leg with no venous insufficiency (1) immediately after injection, (2) 40 seconds after injection, and (3) note the contrast material completely disappeared 3 minutes later.

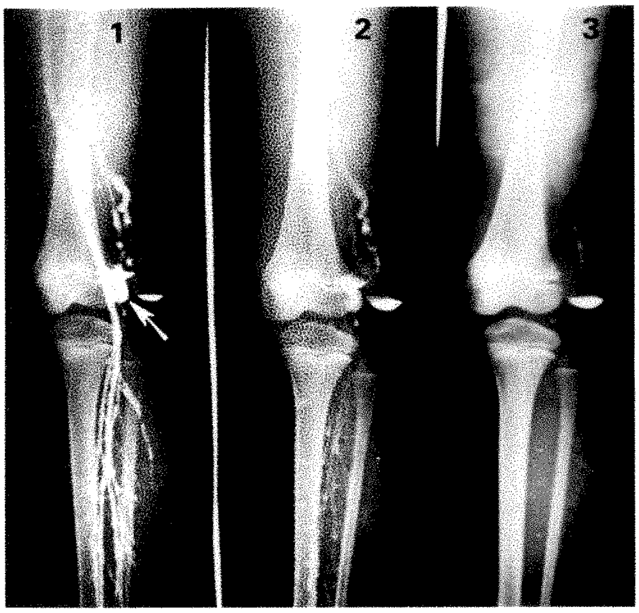

FIG. 2A. Selective ascending functional phlebography in a 5-year-old girl demonstrates reflux through a typical short communicant (arrow) from normal deep veins into a peripheral venous malformation: 0, 40 seconds, and 3 minutes after injection represent 1, 2, 3, respectively. Three minutes after injection (3), there is retention of some contrast material compatible with first-degree venous insufficiency.

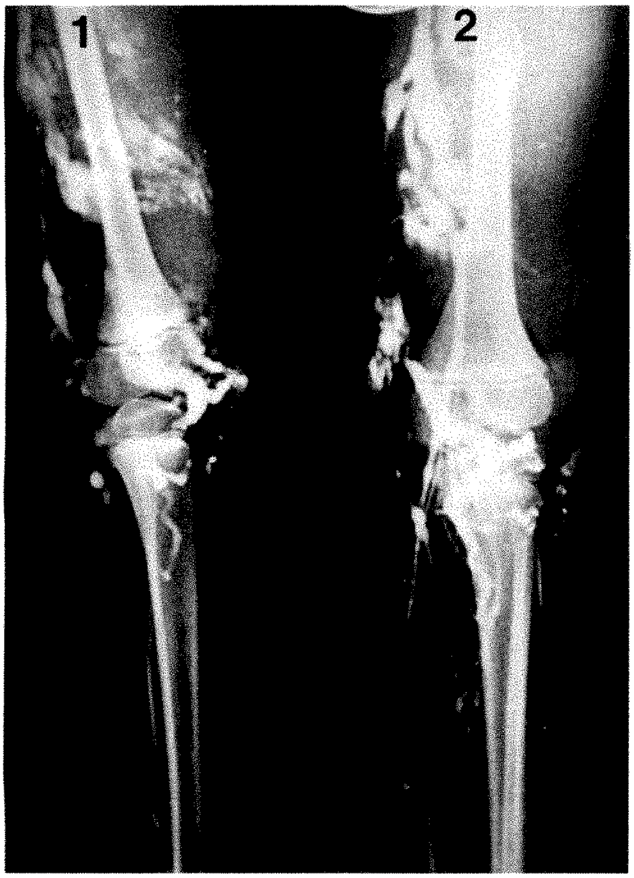

FIG. 1B. Superficial nonfunctional phlebography in the patient described in Figure 1A demonstrates spongy venous mass, a typical peripheral angiodysplastic lesion (2 projections).

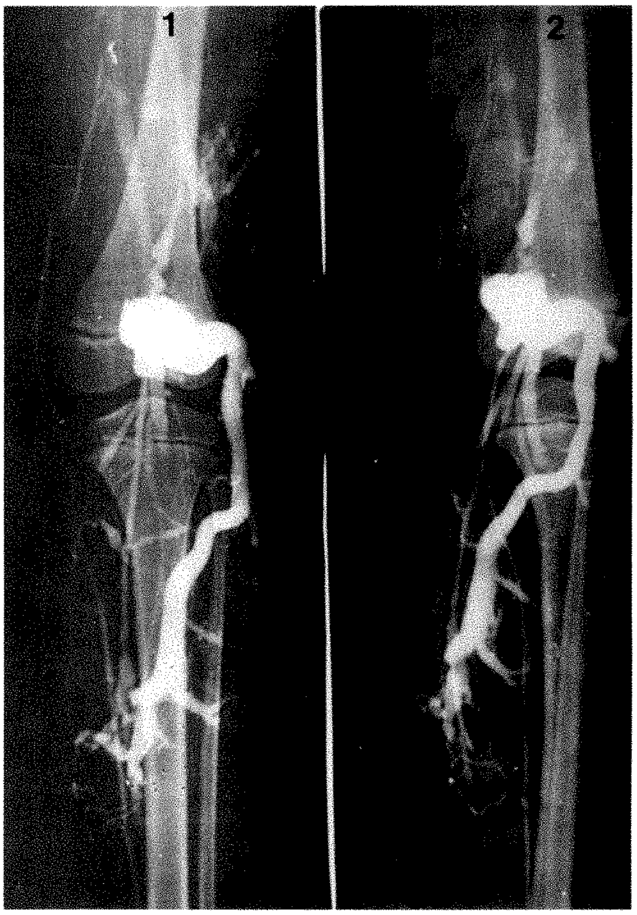

FIG. 2B. Superficial nonfunctional phlebography (in 2 projections) in the patient described in Figure 2A demonstrates peripheral angiodysplastic formation that resembles segment of persistent embryonal vein.

TABLE 3. *Functional and Morphologic Phlebographic Findings in 10 Patients with SVS Angiodysplasia and Abnormal Deep Venous System*

	No. of patients
Venous reflux	9
Typical communicants	1
Atypical very short communicants	8
Venous insufficiency	5
First degree	1
Second degree	2
Third degree (Fig. 3)	2
Deep veins abnormalities	10
Saccular aneurysms of politeal or femoral veins	4
Fusiform aneurysms of tibial or calf veins	3
Aplasia of superficial femoral vein	3
Morphologic variations	10
Intramuscular calf angiodysplasia	3
Subcutaneous angiodysplasia	3
Intramuscular thigh and knee joint angiodysplasia	2
Intramuscular thigh angiodysplasia	1
Intramuscular and subcutaneous angiodysplasia	1

TABLE 4. *The Surgical Treatment of SVS Angiodysplasia (18 Patients)*

Procedure	N
Excision of intra- and subcutaneous lesions	9
Excision of subfascial lesions	14
Inter- and intramuscular	2
Knee joint	5
Ankle joint and foot	5
Neurolysis	2
Total	23

eurysms (4 patients), fusiform aneurysms (3 patients), and aplasia of the superficial femoral vein (3 patients) were the major abnormalities encountered. In this group, there was significant reflux from the deep venous system into the superficial venous malformations, mainly *via* atypical ultrashort communicating veins (Fig. 3). Venous insufficiency demonstrated in five patients of this group was more severe than that observed in patients in group A. There was no difference in the morphologic features and the extent of the angiodysplastic lesions in both groups. None of the patients had involvement of the greater or the lesser saphenous veins.[8]

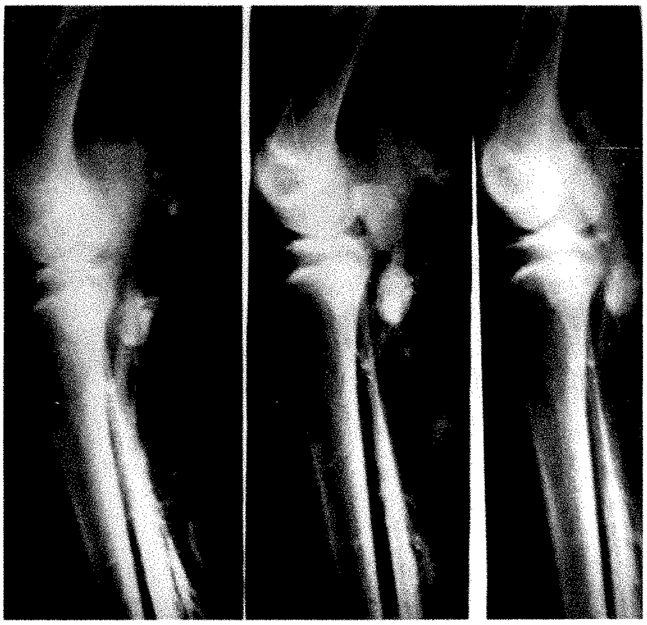

FIG. 3. Selective ascending functional phlebography in a 14-year-old boy demonstrates a rapid opacification of a peripheral angiodysplastic spongy malformation filled *via* multiple ultrashort invisible communicating veins. Three minutes after injection (3), there is still considerable retention of contrast material, third-degree venous insufficiency (the timing is identical to that of Fig. 1A).

Surgical Treatment

Eighteen patients underwent excision of the angiodysplastic lesions and ligation of the adjacent communicating veins (Table 4). Four of these patients required more than one session. The cosmetic and the functional results were very good in patients with mild and moderate forms of the disease. Patients with severe functional disability had temporary relief. The main clinical and venographic features of the different forms of SVS angiodysplasia and the results of treatment are summarized in Table 5.

Discussion

Congenital angiodysplasia is a well-recognized clinical entity. All the patients in the current series belonged to a more defined clinical and radiologic entity, namely venous angiodysplasia.[4–6] These malformations are structural anomalies with errors of vascular morphogenesis resulting in gradual venous dilatation and formation of collaterals or shunting vessels.[2]

Venous angiodysplasia may present either as venectasia or as spongy masses.[4–6,8] The venectasia may vary from dilatation of the skin capillaries (port wine stain) to formation of giant, valveless venous trunks resembling remnants of embryonic veins. The most common presentation of these lesions is a conglomeration of dilated tortuous venous trunks.

The spongy masses are actually smooth cavernous spaces lined with normal endothelium and surrounded by connective tissue and muscular elements similar to those observed in a normal vein. The cavernous spaces occasionally contain thrombi or calcified phleboliths.[5,6]

The extension of the venous lesions varies from an intracuticular or subcutaneous (superficial to the fascia

TABLE 5A. *Clinical Features of the Different Forms of Severity of SVS Angiodysplasia*

Severity	No. of Patients	Symptoms	Clinical Findings	Anatomic Level of the Angiodysplastic Lesions
Mild	11	Asymptomatic	Intracuticular lesions (port wine stain), subcutaneous varicosities	Intracuticular Subcutaneous
Moderate	8	Localized pain	Prominent varicosities, venous lump	Subcutaneous, subfascial
Severe	5	Disabling pain, swelling	Swollen extremity, painful venous lump, hemarthrosis, muscle atrophy	Subfascial

propria) location to subfascial involvement, *i.e.*, intermuscular, intramuscular, synovial with joint involvement, or intraosseous lesions.[4] Most of the patients have bi- or tri-level involvement.

The venous drainage of the normal lower extremity consists of three main systems: deep, superficial, and communicating veins network. This classification is frequently unsatisfactory in defining the abnormal location and extension of the congenital venous abnormalities. Therefore, we have simplified the classification of venous angiodysplasia and divided these lesions into two groups: (1) malformations of the deep venous trunks (DV), which are the major draining veins of the lower extremity; (2) malformations of the superficial veins (SVS), including all veins located superficially or deeper to the deep fascia. All the patients in the current series had malformations of the SVS. In addition, 10 had significant pathologic features of the deep venous system (DV). The existence of combined SVS and DV pathologic features has been described by several authors.[9–11] The presence of conglomerates of superficial varicose veins atypically located on the lateral aspect of the lower extremity is not diagnostic but suggestive of a possible involvement of the deep venous system. The use of selective ascending functional phlebography is mandatory for an anatomic and functional assessment of this complex abnormality.[8,12] Any attempt to ligate or excise the superficial varicose veins, which are the main alternative draining routes in this situation, will compromise the affected limb.[4,11–13]

The communicating venous system plays a major role in the clinical course and the final outcome of SVS angiodysplasia.[14] Venous reflux is encountered particularly in patients with atypical communicating veins. Three forms of atypical communication were previously described: (1) persistent long embryonic venous trunks, (2) single short communicants, and (3) numerous ultrashort communicants.[7] Single short communicants in six patients (Fig. 2A) and numerous ultrashort communicants in seven patients (Fig. 3), were the major routes of venous reflux from the deep venous system into the superficial angiodysplastic malformations. In our experience, meticulous ligation of the typical and atypical communicating veins improves the cosmetic results and the long-term outcome of the surgically treated patients. The ultrashort communicants preclude successful removal of angiodysplastic formations since they are too small and numerous to be occluded surgically.

Selective ascending functional phlebography is our preferred method to assess the degree of venous insufficiency in patients with congenital venous malformations.[7,12] The majority of the patients (19 patients) in the current series had a well compensated venous return (Fig. 1A). However, four patients with combined deep and superficial veins pathology had second- and third-degree venous insufficiency. One patient with normal

TABLE 5B. *Venographic Features of the Different Forms of Severity of SVS Angiodysplasia*

Venographic Findings				
Deep Veins	Reflux	Venous Insufficiency	Treatment	Results
Normal	Absent or mild	Absent	Observation or complete excision of lesion	Excellent
Normal or aneurysms	Via typical or atypical short communicants	Absent or first degree	Complete or partial excision with ligation of the incompetent communicating veins	Satisfactory or very good
Normal or aneurysms or aplasia	Via multiple ultrashort communicants	Second or third degree	Partial excision, supportive elastic bandage	Poor or Satisfactory

deep venous system had a second-degree venous insufficiency due to extensive SVS angiodysplasia involving the entire thigh muscles and the knee joint (Fig. 3).

The main clinical and venographic features of SVS angiodysplasia are summarized in Tables 5A and B. The classification of the patients into three groups according to the severity of the disease (mild, moderate, and severe) is helpful in planning the appropriate conservative or surgical treatment. It should be emphasized that the morphologic appearance of SVS angiodysplasia lesions is identical in the three forms of the disease. On the other hand, local swelling, pain, muscle atrophy, presence of deep angiodysplastic lesions, venous reflux *via* atypical communicants, and the presence of deep venous abnormalities with venous insufficiency have a poor prognosis.

We recommend that any therapeutic approach applied to this rare and complex entity should be based on the complete clinical, anatomic, and functional workup to prevent serious and even life-threatening complications.

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Results of Surgical Correction of Anorectal Malformations

A 10–30 Year Follow-up

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Of 119 patients with surgical correction of anorectal malformations, 47 who were 10–30 years of age were interviewed personally and had manometric studies to evaluate postoperative continence. This clinical study included not only long-term anorectal function but also sexual function. Patients with low type anomalies or with intermediate type anomalies were more likely to be continent, whereas patients with high type lesions had some problems with continence. However, only two of the 16 patients (12%) with high type anomalies were classified as having poor results. This rate is perhaps lower than might be expected. Thus, incontinent patients may become continent even if they were classified as having fecal incontinence before 6 years of age. Most patients who were 15–30 years of age had normal sexual function except for two females with irregular menstruation. These results indicate that achievement of fecal continence and sexual function in patients with high type anomalies treated by abdominoperineal rectoplasty depends on careful dissection as close as possible to the rectal wall and bringing the terminal bowel down exactly within the sling of the puborectal muscle.

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THE MAIN OBJECT OF any surgery for anorectal malformations is to achieve anal continence. In addition to bowel function, sexual function is also important. However, very few reports[1,2] have mentioned sexual function after surgery for anorectal malformations.

This paper reports the long-term results with regard to bowel and sexual functions in patients treated surgically for anorectal malformations who are now 10–30 years of age.

Clinical Data

One hundred forty-one patients with anorectal malformations were treated at the Children's Research Hospital of Kyoto Prefectural University of Medicine from 1960 to 1986 (Table 1). Of these patients, 66 (51 males and 15 females) had high type anomalies, 24 (16 males and 8 females) had intermediate type anomalies, and 51 (34 males and 17 females) had low type anomalies.

A total of 121 surgical corrections were performed on 119 patients (Table 2). Two of the 121 patients had undergone cut-back anoplasty in the neonatal period and anal transplant at 2 or 3 years of age.

The usual operative procedure in this division has been colostomy for the high and intermediate types in the neonatal period, followed by abdominoperineal rectoplasty, in which the rectum was dissected carefully along the rectal wall to preserve the pelvic nerves. The sling of the puborectal muscle was well identified by causing contraction of the puborectal muscle with an electric stimulator, and the pelvic floor was pushed upward from the perineal side by the surgeon's left hand so that the sling of the puborectal muscle could be well visualized. The center of the external sphincter muscle was also identified by causing contraction of the muscle with the electric stimulator. Low type anomalies were treated by neonatal perineoplasty. Anal transplants were performed at 3 or 4 months of age after anal dilatation, or cut-back anoplasty was performed soon after birth, followed by an anal transplant at 2–3 years of age.

Postoperative complications (Table 3) were observed in 31 patients (26%). Prolapse of the rectal mucosa occurred in 14 patients, and the excess rectal mucosa required trimming in all 14 patients. Anal stricture was present in eight patients, leading to secondary megacolon in two patients. Three of the eight patients required

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TABLE 1. *Types of Anorectal Malformations (1960–1986)*

Malformations in Male Patients	No. of Cases	Malformations in Female Patients	No. of Cases
High			
Rectourethral fistula	36	Rectovaginal fistula	7
Anorectal agenesis without fistula	7	Rectovesical fistula	1
Rectovescial fistula	4	Rectocloacal fistula	3
Cloacal extrophy	3	Cloacal extrophy	2
Unknown	1	Unknown	2
Total	51 (13 deaths)		15 (5 deaths)
Intermediate			
Anal agenesis without fistula	9	Anal agenesis without fistula	1
Rectobulbar fistula	6	Rectovestibular fistula	3
Anorectal stenosis	1	Rectovaginal fistula (low)	3
		Anorectal stenosis	1
Total	16		8 (1 death)
Low			
Anocutaneous fistula	26	Anovestibular fistula	10
Covered anus–complete	8	Anovulvar fistula	5
		Covered anus–complete	1
		Perineal canal	1
Total	34		17

secondary anoplasty since anal dilatation was not effective. Intestinal obstruction due to adhesions was present in four patients after abdominoperineal rectoplasty, and all four patients recovered after surgical division of the adhesions. Bowel retraction after pull-through occurred in two patients and recurrent rectovaginal fistula occurred in one patient.

TABLE 2. *Surgical Corrections in 119 Patients with Anorectal Malformations*

Surgical Correction	No. of Patients Male	Female	Total
Staged abdominoperineal rectoplasty	49	11	60 (50%)
Anal transplant	—	10 (2)	10 (8%)
Perineoplasty: perineal anoplasty	6	2	8 (6%)
Cut-back anoplasty	31	12	43 (36%)

TABLE 3. *Complications of Treatment in 119 Patients with Anorectal Malformations*

Complications	No. of Cases
Prolapse of rectal mucosa	14 (12%)
Anal stricture	8 (6%)
Intestinal obstruction	4 (3%)
Secondary megacolon	2 (2%)
Bowel retraction after pull-through	2 (2%)
Recurrent rectovaginal fistula	1 (1%)
Total	31 (26%)

TABLE 4. *Types of Anomaly and Age at Time of Follow-up Assessment*

Type of Anomaly	No. of Cases	Age (Years)	(Mean ages)
High type	16	10–20	(12)
Intermediate type	13	10–24	(13)
Low type	18	10–30	(13)

Current Bowel Control

Forty-seven patients, 10–30 years of age, were interviewed personally and assessed clinically: 16 patients, 10–20 years of age, with high type anomalies, 13 patients, 10–24 years of age, with intermediate type anomalies, and 18 patients, 10–30 years of age, with low type anomalies (Table 4).

Function was evaluated by the Kelly score system[3] on the basis of three criteria: (1) control of feces and bowel habits, (2) fecal staining, and (3) sling action of the puborectal muscle. The results were classified as good (Kelly 5–6), fair (Kelly 3–4), and poor (Kelly 0–2).

The current bowel control of these patients is shown in Table 5 All 18 patients with low type anomalies had good control, and of the 13 patients with intermediate type anomalies, 10 (77%) achieved good control. On the other hand, only seven of the 16 patients with high type anomalies had good control, and two of them (12%) had poor control.

Manometric assessment was usually performed without anesthesia, except in restless children who required mild sedation. The probe was perfused with a constant infusion of 10 ml/h. Of the 47 patients assessed clinically, 41 had manometric studies to evaluate postoperative continence. The results are summarized in Table 6.

All of the 14 patients with low type anomalies had both a high pressure zone in the anal canal and an anorectal reflex. Of the 12 patients with intermediate type anomalies, 11 (92%) had a high pressure zone and six (50%) had an anorectal reflex. Of the 15 patients with high type anomalies, however, 11 (73%) had a high pressure zone and only three (20%) had an anorectal reflex.

Sexual Function (Tables 7 and 8)

Five male patients, 15–20 years of age, were interviewed regarding their sexual function: erection, ejaculation, and history of marriage. All five patients had normal erections and ejaculations. One patient was married and enjoyed normal sexual activities.

Seven female patients, 15–30 years of age, were interviewed regarding menstruation and history of marriage. Five of the seven had regular menstruation, and two had irregular menstrual periods; one had had a rectocloacal fistula and the other had a rectovaginal fistula. Three patients were married, and one had had a normal pregnancy and delivery.

TABLE 5. *Clinical Assessment and Type of Anorectal Malformation*

Type of Anomaly	No. of Cases	Clinical Assessment: Good	Fair	Poor
High	16	7 (44%)	7 (44%)	2 (12%)
Intermediate	13	10 (77%)	3 (23%)	0
Low	18	18 (100%)	0	0

TABLE 6. *Results of Anorectal Manometry*

Type of Anomaly	No. of Cases	Anorectal Manometry: Presence of HPZ	Presence of Anorectal Reflex
High	15	11 (73%)	3 (20%)
Intermediate	12	11 (92%)	6 (50%)
Low	14	14 (100%)	14 (100%)

HPZ = high pressure zone.

Discussion

Specific complications of surgery were observed in 31 of 119 (26%) patients who had had surgical treatment for anorectal malformations. This rate is somewhat lower than that in series of Hecker et al.[4] Anal strictures were especially less frequent, presumably because of careful anal dilatation begun 2 weeks after operation. On the contrary, the rate of mucosal prolapse in our series was 12%, which is almost three times that in the series of Hecker et al. The goal of a cosmetically satisfactory anal opening as well as one that functions normally depends primarily on the operative technique. Therefore, care should be taken to slide the perianal skin flap into the new anal canal so that mucosal prolapse is avoided.

In the current series poor results were not observed either in patients with intermediate type anomalies or in those with low type anomalies. However, two of the 16 patients (12%) with high type anomalies had poor results, and the remaining 88% had good or fair results. In our previous report,[5] 23% of those with high type anomalies had poor results, but the mean follow-up period was 5.75 years. Therefore, this repeat clinical assessment demonstrates that incontinent patients may become continent even if they had fecal incontinence before 6 years of age. Smith et al.[6] stressed the importance of parental assistance in training and of the patient's desire, cooperation, and mental ability. Intellectual development after six years of age through the experiences of school life is one of the steps towards the achievement of continence, in addition to physiotherapy.

We previously reported that continent patients characteristically had a very high pressure zone in the anal canal. Therefore, in view of the current manometric evidence, a high pressure zone and an anorectal reflex were considered to be chief parameters for objective assessment. A high pressure zone was present in 73% of the high type anomalies. This finding correlates well with the clinical evaluation, in which 88% of the patients with high type anomalies had good or fair results. On the other hand, only 20% of the patients with high type anomalies had an anorectal reflex. In our previous study, 20% of the patients with high type anomalies had an anorectal reflex. These results suggest that high pressure zones might be achieved in patients with good or fair results by contractions of the voluntary muscles as intellectual development progresses or as a result of physiotherapeutic training.

TABLE 7. *Sexual Function in Male Patients*

Case	Age (Years)	Type of Anomaly	Erection	Ejaculation	Marital Status
1	18	High	Normal potency	Normal	Single
2	15	High	Normal potency	Normal	Single
3	20	High	Normal potency	Normal	Married
4	17	Intermediate	Normal potency	Normal	Single
5	20	Low	Normal potency	Normal	Single

TABLE 8. *Sexual Function in Female Patients*

Case	Age (Years)	Type of Anomaly	Menstruation	Marital Status
1	17	High	Irregular	Single
2	15	High	Regular	Single
3	17	Intermediate	Irregular	Single
4	24	Intermediate	Regular	Married
5	16	Low	Regular	Single
6	25	Low	Regular	Married (1 child)
7	30	Low	Regular	Married

Sexual dysfunction after major rectal surgery in adults is extremely common.[7,8] In the current study, however, most of the patients with anorectal malformations had normal sexual activity except for the two patients with irregular menstruation. Nixon and Puri also reported that all patients examined had normal sexual activity except for one patient with a permanent colostomy.[1] These results indicate that in the surgery of anorectal malformations, refinements of surgical technique, such as dissection as close as possible to the rectal wall, can prevent postoperative sexual disturbances. Therefore, the majority of patients with anorectal malformations can expect a good quality of sexual activity.

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Varicocele in Youth

A Therapeutic Dilemma

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The need for treatment of asymptomatic varicocele in youth is controversial. In the current study testicular volume and seminal variables were evaluated in three groups: young varicocele patients with undetermined fertility potential, infertile varicocele patients, and a control group of young males. The testicular volume was determined by ultrasonographic measurements. The results revealed a significant loss of "testicular mass" in both varicocele groups compared with the control group. The seminal findings disclosed a severe disturbance of spermatogenesis in the older varicocele group, whereas in the younger varicocele patients only the total spermatic count was significantly depressed. This difference in severity of functional impairment between the younger and older varicocele groups possibly points towards progressiveness of damage to the testicles. A more decisive therapeutic approach to the young male with asymptomatic varicocele and unknown fertility status could be justified.

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VARICOCELE IS CONSIDERED by most authors as the most frequent treatable cause of male infertility,[1,2] although there are a few reports to the contrary.[3,4]

The impaired testicular function in the infertile male with varicocele is expressed by deranged seminal findings,[5] histologic changes,[6] and decreased testicular size.[1,7] Recent studies stress the prognostic value of testicular volume in patients who have surgical treatment of varicocele.[8] Testicular volume and tonometry (consistence) were positively correlated with semen quality.[9]

Due to the ample evidence connecting varicocele and infertility, most clinicians do not hesitate as to the active approach when confronted by a patient in this setting. However, controversy exists over the appropriate management of the very young male whose varicocele is an incidental finding and his fertility potential is still unknown.

Interestingly, idiopathic varicocele is a neglected entity in classic pediatric and pediatric–urology texts,[10] yet vast epidemiologic studies involving thousands of children and adolescents revealed that the incidence of varicocele is comparable to that of the adult male population.[10–13] An explanation for this lack of preoccupation by pediatric clinicians regarding this common condition (incidence of approximately 15% in large series), is that pediatricians usually perform examinations with the children lying down. Varicocele tends to disappear in the supine position and thus the genitalia are not examined thoroughly enough.

Several recent studies of children and adolescents with varicocele came up with findings that can be termed "alarming": a sharp decrease in size of the left testicle was noted in 74%, 77%, and 81% of these boys in three separate studies.[11,12,14] Furthermore, 90% of testicular biopsies performed in two series of prepubertal and pubertal boys revealed histologic findings consistent with disturbed spermatogenesis, similar to those described in infertile adults with varicocele.[12,15]

The current study was done to provide controlled data concerning the question whether or not the fertility potential is already endangered in the very young male with varicocele.

Materials and Methods

The testicular volume and seminal variables were tested and compared in three groups of patients: (1) "young varicocele" group—21 patients, age range 16–23 years, mean age 19 years. All had unilateral left varicocele diagnosed clinically, with unknown fertility

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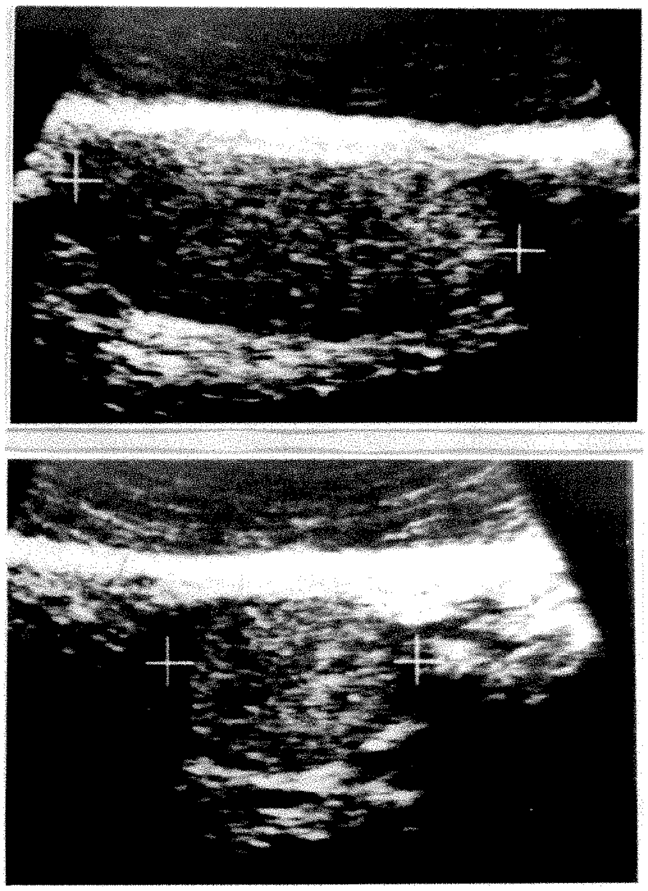

FIG. 1. Scanning planes used in measuring the testicular volume (10-MHz high-resolution transducer). *Top.* Longitudinal plane (the length value). *Bottom.* Transverse plane (the width and thickness values).

status, without previous significant urogenital diseases, trauma, or surgery in the genital area. Normal hormonal status was assumed by a well developed male habitus. (2) "varicocele infertility" group—18 patients, age range 25–38 years, mean age 30 years. These patients were referred from the Infertility Clinic after evaluation of sterile marriage. A left varicocele was the only pathologic finding in these otherwise healthy males. (3) control group—18 young males, age range 16–38 years, mean age 25 years. They were referred to surgery because of minor disorders completely unrelated to the urogenital system. No genital abnormalities were found on physical examination. They were randomly assigned for the study, and thus some of them fathered children, whereas in others the fertility potential was still unknown.

TABLE 1. *Testicular Volume Determinations*

	Mean Right Testicular Volume (ml)	Mean Left Testicular Volume (ml)	Difference Between Right and Left Mean Volumes (ml)
Young varicocele group	11.95	9.50	2.45 ($p < 0.001$)*
Varicocele infertility group	12.10	9.21	2.89 ($p < 0.001$)*
Control group	15.48	14.46	1.02 (not significant)

* Student's t-test.

Ultrasonographic Determination of Testicular Volume

The examinations were performed using the following equipment: real-time unit Dynex (Elscint, Haifa, Israel) with 5-MHz and high-resolution 10-MHz transducers; real-time unit Sonoline-8000 (Siemens, Erlangen, West Germany) with 7-MHz transducer; and a B-mode gray-scale ultrasound (Picker, Northford, USA) with a 5-MHz transducer.

Examinations were performed with the patient in the supine position on both sides by the "gloved hand" technique, obtained by direct contact of the transducer with the scrotal skin.[16] Sagittal and transverse scanning planes were used to measure the volume of each testis. Volume determinations were made using the formula for the volume of an ellipsoid:

$$0.523 \times \text{length} \times \text{width} \times \text{thickness}^{17} \quad \text{(Fig. 1)}$$

Seminal Parameters

In the "young varicocele" and "control" groups only one semen specimen was examined due to technical difficulties in obtaining multiple specimens in these patients. The abstinence period was at least 3 days. In the "varicocele infertility" group, multiple samples were available. The following variables were evaluated: (1) total sperm count; (2) motility index (% motility × grade); and (3) morphology (by the light microscopy score).

Statistical Analyses

The testicular volume values, seminal morphology, and motility index were analyzed using the Student's t-Test. The total sperm counts were evaluated by the Mann-Whitney nonparametric test because of unbalanced data.

Results

Testicular Volume

In each group the mean volume for left and right testicles and the difference between both were calculated. The volumes were strikingly similar in both varicocele groups (Rt—11.95 ml and 12.10 ml; Lf—9.50 ml and 9.21 ml), compared with the control group (Rt—15.48 ml, Lf—14.46 ml) (see Table 1).

Mean testicular mass, being the sum of right and left mean volumes, was calculated for each group. The values were statistically compared among the groups showing that the testicular mass in both varicocele groups was significantly smaller than in the control group, whereas there was no difference between the varicocele groups compared with each other (see Table 2).

Seminal Findings

The variables tested displayed no significant difference in motility index and morphology between the control and young varicocele groups; however, some difference showed when the total sperm counts were compared ($p < 0.01$).

When the control group was compared with the varicocele infertility group the difference was statistically significant in all variables evaluated. Some slight difference showed in the motility index only between the varicocele groups (see Tables 3 and 4).

TABLE 2. *Mean Testicular Mass*

Groups Compared	Mean Testicular Mass Values (ml)	Significance of Difference
Control *versus* young varicocele	29.94/21.45	$p < 0.001$*
Control *versus* varicocele infertility	29.94/21.31	$p < 0.001$*
Young varicocele *versus* varicocele infertility	21.45/21.31	Not significant

* Student's t-test.

TABLE 3. *Total Sperm Counts*

Group	Range	Mean
Control	26×10^6–418×10^6	186×10^6
Young varicocele	0.2×10^6–260×10^6	71×10^6
Varicocele infertility	0.2×10^6–139×10^6	35×10^6

Discussion

The age range in our groups of patients was between 16 and 38 years. We excluded younger children and older men (although we treated several varicocele patients 12–16 years of age), so as to include in the study only fully developed gonads (postpubertal) and before any functional decline could be attributed to advanced age.

Testicular volume is generally assessed by different kinds of orchiometers or calipers.[1,8,9,18] In these methods the size of the testicle is measured including the scrotal skin, testicular envelopes, and differing amount of fluid in the tunica vaginalis. In studies using ellipsoid rings being compared with the testis, the subjective impression of the examiner is an additional factor of inaccuracy. Our method of ultrasonographic determination of the volume measures accurately the testicular tissue mass only. This fact could account for the smaller values in our patients compared with figures in the literature (20–25 ml normal adult volume).[1,8,18]

The fact that in the control and the young varicocele groups, only one seminal sample was analyzed is a drawback. However, it is countered by the fact that we consider mean, collective data while comparing the groups. Thus, the individual fluctuations in seminal variables that could arise on repeated examinations should not significantly affect the general trend in any given group.

Our current data reveal that the left testicle is significantly smaller than the right in both the young varicocele and varicocele infertility groups, which is in sharp contrast to the control group. Moreover, the values of volumes of both testicles in the varicocele groups are strikingly similar, despite that in the young varicocele group the patients are significantly younger (mean age: 19 *vs.* 30 years in the infertile group) (Table 1). When we compare the testicular mass, there is a significant difference between the control group and the two varicocele groups, whereas no difference is found between both varicocele groups (Table 2).

It seems, therefore, that in the young males with varicocele and unknown fertility potential, there already exists a significant loss of testicular mass similar to older varicocele patients with known fertility problems.

When we consider the seminal findings (Tables 3 and 4), it is obvious that in the varicocele infertility group all variables are significantly depressed compared with the control group; most prominent are the disturbance in motility and total count, less in morphology. However, in the young varicocele group, the only significantly de-

TABLE 4. *Differences in Seminal Findings*

Groups Compared	Difference Among Groups: Motility Index	Difference Among Groups: Morphology	Difference Among Groups: Total Sperm Count
Control *versus* young varicocele	None	None	Significant ($p < 0.01$)†
Control *versus* varicocele infertility	Significant ($p < 0.001$)*	Significant ($p < 0.05$)*	Significant ($p < 0.002$)†
Young varicocele *versus* varicocele infertility	Significant ($p < 0.01$)*	None	None

* Student's t-test. † Mann-Whitney nonparametric test.

pressed variable is the total sperm count. Some slight disturbance can be detected in the motility index. All these findings suggest that a correlation exists between decrease in testicular mass and disturbed spermatogenesis. This is consistent with some previous observations; it was claimed that the "total testicular volume yields a reasonable estimate of the total quantity of testicular tissue available for spermatogenesis."[8] Another author reported that "mean testicular volume can be strongly correlated with sperm counts."[18]

Our data also suggest that the detrimental effect of varicocele on testicular function is progressive. The fact that in our study the seminal variables were more disturbed in the older varicocele group compared with the young varicocele patients, could support this assumption. Although Lipshultz and Corriere found progressiveness of testicular atrophy in varicocele patients,[7] in our current study the loss of testicular mass was already well established in the young varicocele group, being similar to that existing in the older patients.

In this context it should be noted that in the few studies of children with varicocele, left testicular hypotrophy was a constant finding, being most pronounced and prevalent in the prepubertal age group.[11,12,14] These authors suggest that testicular hypotrophy in varicocele is in fact testicular growth arrest caused by an unknown mechanism during the most critical period of testicular growth and development, the pubertal years. The findings of histologic changes consistent with disturbed spermatogenesis in young boys with varicocele should not be forgotten either.[12,15]

These considerations supported by our current data suggest that an active therapeutic approach to the young male with varicocele could be justified, even in asymptomatic patients with fertility potential still unknown.

There is ample evidence proving that the basic physiologic disturbance in varicocele is the reversal of flow in the venous drainage system of the testis, and thus the modern therapy of varicocele aims at abolishment of this reflux. The classic surgical procedure described in 1918 by Ivanissevitch and modified by Palomo,[19] consists of high ligation of the internal spermatic vein along its retroperitoneal course. Recently, a nonoperative method of percutaneous venographic embolization of the internal spermatic vein and its main collaterals has been introduced. However, we have shown previously that the internal spermatic vein incompetence is not the only source of reflux in some cases of varicocele. In a considerable percentage of patients, a hemodynamic derangement in the external (cremasteric) spermatic vein can be demonstrated as well.[20] In these "combined reflux" cases the classic operation of high ligation of the internal spermatic vein or percutaneous embolization could be inadequate and thus could account for the surgical and spermatologic failures.[21] Accordingly, we described a transinguinal operative approach permitting simultaneous ligation of the internal and external spermatic venous systems.[22] Currently, a prospective evaluation of these three methods of treatment (the classic high ligation operation, the transinguinal simultaneous ligation, and the embolization) is being conducted in our department.

The offensive factor causing the functional and histologic damage to the testes in the presence of varicocele has not been conclusively identified yet. Whether it is a derangement in temperature regulation or some "mysterious toxic" substance brought by the venous reflux, the fact is that an effective abolishment of this hemodynamic disorder ameliorates in a considerable percentage of patients the testicular function as reflected by spermatologic variables, and even augmentation of the testicular mass.[4,8,15,18]

There are two other pathologic conditions commonly affecting the male gonads in the pediatric age group: the undescendent testis and testicular torsion. In these disorders, even if a unilateral lesion is present and even if it is promptly treated surgically, the incidence of later infertility is significantly higher than in the general male population. Here, just as in varicocele, it is still unknown why a unilateral testicular pathology should affect the function of both testicles. It was already suggested that this detrimental sympathetic effect of the diseased testicle on the healthy one would be aborted by performing early orchiectomy instead of orchipexy in cases of cryptorchidism or torsion. Whether a similar suggestion could be made by analogy in varicocele is a hypothetical or perhaps a philosophical question at the current stage of the state of arts. It should not be ignored that here we have more conservative and effective modes of treatment, which is not the case in infertile males who had testicular torsion or undescendent testis in childhood. However, this question is challenging enough to be tested by an experimental study in laboratory animals.

If the detrimental effect of varicocele on testicular function may be progressive as also partially suggested by our seminal variables, a recommendation to undertake a more thorough active screening among schoolage boys could be worthwhile. Whether early identification and treatment of prominent varicoceles accompanied by hypotrophic left testicles could prevent irreversible testicular lesions would be determined by long-term prospective studies.

Acknowledgments

We thank Mr. Isaac Reichbard and Mrs. Lucy Keleman from the Ultrasound unit, Diagnostic Radiology Department, for their technical assistance.

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Book Reviews

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Principles and Practice of Research: Strategies for Surgical Investigators. H. Troidl, W. O. Spitzer, B. McPeek, D. S. Mulder, M. F. McKneally. 380 pp. New York: Springer-Verlag. 1986. $58.00.

THIS BOOK IS UNUSUAL in that the topic of principles and practice of surgical research has not heretofore been analyzed in such a clear, concise manner. The five editors from Canada, the Federal Republic of Germany, and the United States have selected 50 international contributors, all of whom are well known for their educational or scientific accomplishments. The book is divided into six sections, the first of which is entitled "The Rationale of Surgical Research." This is primarily an historical accounting of surgical research and a philosophical discussion of the importance of basic science and clinical science research to a surgical training program. Sections II, III, and IV contain largely practical information and will be of greatest interest to most readers. In Section II entitled "Starting the Research Process" there are contributions on methods of literature review, computer technology, the development of research protocols, the organization of clinical trials, and ethical aspects of research. The chapters "Statistics Demystified" and "Endpoints for Clinical Studies" are especially well done. Section III addresses "Selected Strategies of Research" and is devoted to topics in both experimental animal and clinical experimentation, all of which are of high quality, especially the chapter on "Clinical Research" and "Multicentre Collaborative Clinical Trials." Section IV, "Reporting Your Work," deals with the proper methods of abstract writing, presentation of data, either verbally or in a poster format at national and international meetings, and the chairing of scientific sessions either at large meetings or at closed conferences.

Although most of these chapters are brief, each contains much valuable information. Section V, "International Perspectives on Surgical Research," has contributions by surgical investigators from several countries. The final chapter in this section, "Common Characteristics and Distinctive Diversity in Surgical Research: An International Analysis," is written jointly by the five editors and provides a clear comparative analysis of surgical training programs, expenditures in biomedical research, and research training opportunities for surgeons in nine countries: Canada, England, France, Germany, Japan, Spain, Sweden, Switzerland, and the United States. The final section is titled "Opportunities in Surgical Research." There is a very good chapter on "Future Horizons in Surgical Research" by Dr. Francis D. Moore. It was he who did so well in developing bridges between the laboratory and the bedside, and he eloquently encourages young surgical investigators to concentrate their efforts at this interface if they are to make significant contributions in clinical research.

This is an excellent book, especially for those in surgical residency training programs or for junior faculty members who are just beginning their lives as surgical investigators. The editors have admirably achieved their goal and are to be commended for handling so ably this critically important area of surgery.

SAMUEL A. WELLS, JR., M.D.
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Trachea and Lung Surgery in Childhood, Vol. 21 in the series Progress in Pediatric Surgery. P. Wurnig (Volume Editor). 147 pp. New York: Springer-Verlag. 1987. $75.50.

DESPITE SOME OBSCURITY in translation, the preface to *Trachea and Lung Surgery in Childhood* by Professor Wurnig of Vienna, the volume's chief editor, points out that improvements in respirator therapy and intensive care have led to more frequent observation of congenital and acquired tracheal and bronchial deformities. This book is Volume 21 of the series *Progress in Pediatric Surgery* published by Springer-Verlag and is not intended to be a textbook. It contains 13 contributions primarily on airway disease, and four on pulmonary topics—three of these addressed to sequestration and one to congenital cystic adenomatoid malformation.

A wide variety of airway problems are discussed. These include: subglottic stenosis: congenital and acquired; treatment by laser and by reconstructive surgery; laryngotracheal cleft; tracheal excision and reconstruction for tumor and stenosis; use of cardiopulmonary bypass; and tracheobronchial and pulmonary tumors. The contributors chiefly present their own experiences in each topic, with a lesser effort at comprehensive presentation of the subject. This has the advantage of specificity and concreteness but leaves a little to be desired for the reader not already versed in laryngotracheobronchial surgery. The papers (I will call them that rather than chapters) vary greatly both in quantity of material reviewed (some are single case reports) and breadth of discussion. A certain amount of repetition is inevitable but it is not of such amount that it is troublesome.

The deficits noted actually give a measure of the rarity of these lesions, the difficulty of their management, and the diffusion of experience in management. Thus, there is merit in presenting a small number of cases from the authors' experience, rather than diffuse generalizations that might seem to a general reader to be derived from a much larger experience.

The contributors are from Austria, Finland, Germany, The Netherlands, Norway, and Switzerland. The English is generally clear and easily readable. Some additional editing both with respect to phrasing, word selection, and spelling would have smoothed out the rough spots.

Pediatric airway surgery remains one of the more difficult areas of airway reconstruction, in part due to the small volume of patients treated and in part to the special problems presented by the juvenile airway. This volume is a useful contribution for the surgeon with special interest in the area. For the more general surgical reader, it may serve the educational service of leading him to further study and a cautionary purpose in respect to trying his hand. A broader overview of the field might have made these aspects even clearer.

HERMES C. GRILLO, M.D.
Boston, Massachusetts

Practical Noninvasive Vascular Diagnosis, 2nd Edition. Richard F. Kempczinski, James S. T. Yao. 555 pp. Chicago: Year Book Medical Publishers. 1987. $50.00.

TECHNOLOGICAL ADVANCES in the instruments used for the detection of vascular diseases rapidly render obsolete many devices in an already bewildering array of machines. Easily readable books such as this second edition are of particular value to those not expert in this field.

The book is attractive, with appropriate subdivisions, easy-to-read type, and clear illustrations. The text is divided into five sections: the laboratory, instrumentation, extremity arterial evaluation, cerebrovascular evaluation, and venous evaluation. The contributors to these topics are recognized people in the field, and the presentations have an authoritative tone. The subjects are well covered, and the chapter subdivisions are arranged logically, clearly marked, and presented in similar formats. Each chapter has an appropriate bibliography.

Several chapters will be especially useful to those who need the information the most: the person relatively new to the field, *i.e.*, the young physician or nurse/technologist. Information needed to organize and operate a vascular laboratory will be helpful to anyone entering the area. The recommendations and concepts discussed are timely and pertinent.

The expanded roles of advanced instruments are the main reasons for the second edition. These discussions are complete, especially where concerned with cerebrovascular disease; however, unfortunately there is a great deal of repetition. Even many of the illustrations, especially of wave forms, B-mode images, and spectra, are similar.

The sections dealing with venous disease should resolve some of the current controversies regarding what is actually needed. Modern methods, such as B-mode imaging of veins, are lucidly discussed, and general recommendations described, as well as specific instructions on how best to perform the tests.

This book will be a valuable edition to the library of anyone interested in vascular diseases. Its main target appears to be those who are not already expert, and as such, it is successful in its aim.

MALCOLM O. PERRY, M.D.
Nashville, Tennessee

Clinical Surgery, Volumes 1 and 2. John H. David, William R. Drucker, Roger S. Foster, Jr., Richard L. Gamelli, Donald S. Gann, Basil A. Pruitt, Jr., George F. Sheldon. 3264 pp. St. Louis: The C. V. Mosby Co. 1987. $105.00.

WITH SO MANY EXCELLENT TEXTBOOKS on surgery currently available, why yet another? This question was asked by this reviewer, and by Doctor Davis in his introduction to this two-volume opus. The answer the authors provide is that a survey of undergraduate and postgraduate students and practicing surgeons demonstrated a need for a surgical textbook that took an innovative problem-solving approach.

The seven prominent editors have collected contributions from 101 noted American surgeons and have added their own. The format of *Clinical Surgery* is both different and unique. To accomplish this, these volumes have been divided into seven distinct sections, each addressing a specific component of surgical practice. In Part One, the reader immediately realizes that this is not a run-of-the-mill contribution when he/she discovers chapters on education and certification requirements in the United States today and another on the clinician's role in the cost of health care. The 11 chapters in Part Two comprise a miniphysiology textbook. Part Three is unique in that single problems are addressed; *e.g.*, abdominal pain, weight change, and alterations in blood pressure, to mention but a few. The ensuing sections deal with patient management and diseases of organs and systems. In each of these sections, as in most others, each chapter concludes with a concise summary of all the problems discussed, enabling an excellent rapid review. Emphasizing that trauma is the neglected disease of modern society, a comprehensive section on trauma follows, covering commonly (automobile) and uncommonly (elephants!) encountered injuries. A section on special areas (sepsis, transplantation, plastic and pediatric surgery) complete Volume Two.

Clinical Surgery is a masterful contribution. It will be well received by all students of surgery and will, I believe, establish the format of surgical and medical textbooks of the future.

JON A. VAN HEERDEN, M.B.
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The Psychological Experience of Surgery in the series **In General and Clinical Psychiatry.** Richard S. Blacher. 236 pp. New York: John Wiley & Sons. 1987. $31.50.

IN THIS SLIM VOLUME, Blacher and 11 contributors, liaison psychiatrists for surgical services, present the patient's view of the surgical experience. The stated goal is to share the patient's perspective with surgeons, surgical nursing staff, and other members of the surgical team. The unstated goal is to improve patient care as well as surgical outcome by improving communication between surgeons and their patients.

Keeping the traditional roles of the surgeon and psychiatrist intact, the psychiatrists share their intimate view of day-to-day patient interactions, allowing the surgeon to witness common fears, expectations, and misconceptions. Armed with this additional insight, the surgeon is thus able to recognize subtle signs of depression or irrational fears. The surgeon may then choose to deal with the problem directly or to consult a psychiatric colleague. This early intervention may circumvent the need for psychopharmacologic drugs and prevent progression to a major problem. A strength of this book is the focus on improving the quality of the seemingly inconsequential but powerful interactions between surgeons and their patients, such as explanation of the risks before obtaining informed consent for a procedure. There is no preaching about cold-hearted surgeons; rather the role of a self-assured surgeon to allay the anxieties and fears of the patient is underscored.

This 13-chapter volume would be improved by judicious editing. Although the chapters ostensibly focus on a specific aspect of surgery, such as bypass surgery for superobesity or lower limb amputation, important information relevant to *all* types of surgery is found in each chapter. It is worth the extra time to read through the book to find all the useful bits of information, regardless of whether the topic is of specific interest to the reader. For instance, the chapter on gynecological surgery contains a lucid discussion of the emotional impact of surgery involving sexual/reproductive organs and the attendant difficulties for a patient in discussing their concerns. The three chapters by Dr. Blacher are largely redundant. Although the material presented contains helpful suggestions for improved communication with and care of surgical patients, it is not apparent to this reader whether the repetition increased retention. The chapters on brain surgery, denial in cancer surgery and burn victims are not written with the surgeon-reader in mind; rather they are addressed to fellow liaison psychiatrists and do not fit conceptually with the rest of the material.

A final comment is that some of the clinical material emphasizes the dramatic rather than the commonplace, contradicting the authors' stated goal. This is particularly noticeable in the chapter on renal disease and transplantation. It contains a sensitive, thoughtful treatment of chronic illness and of the psychological aspects of receiving a donated organ and then describes a case wherein a 10-year-old boy commits suicide after learning that his estranged father donated his transplanted kidney.

RANDY L. GELLMAN, M.D.
New Haven, Connecticut

Cancer in the Neck: Evaluation and Treatment. David L. Larson, Alando J. Ballantyne, Oscar M. Guillamondegui. 280 pp. New York: Macmillan Publishing Co. 1986. $68.00.

THIS MULTIAUTHORED BOOK (44 authors) is edited by three head and neck surgeons from MD Anderson Hospital and Tumor Institute in Houston.

The six sections of the book are divided into two categories; they are devoted to basic immunobiological and clinical research. The original and innovative concepts of tumor immunobiology have been previously published and promulgated by Garth L. Nicholson, Professor and Chief of Tumor Biology at the MD Anderson Tumor Institute. These forward-thinking projections concerning the mechanisms of metastasis are worth the modest price of the book. The remaining sections on evaluation of neck specimens, radiotherapeutic considerations, neck dissection alternatives, chemotherapeutic considerations, and management of neck melanoma and unusual tumors of the neck are a conglomerate of confusing, unhelpful controversies based on personal biases.

The rationale for some approaches to therapy advocated by some of the authors lack reason and are based on false logic. This book fulfills all expectations of weakness anticipated in an uncoordinated, multiauthored text presenting retrospective studies of limited value.

Perhaps the most unredeeming tragedy is that a recognized, skilled group of surgeons at the MD Anderson Medical Center failed to communicate and develop what could have been one of the world's most outstanding prospective studies with a little cooperation.

One interesting and redeeming feature in this book is the thoughtful editorial comments that initiate each chapter.

This book will have limited influence on the practicing head and neck surgeon and can only confuse the novice resident. I recommend checking it out of the library for reference and for its extensive bibliography.

PAUL H. WARD, M.D., F.A.C.S
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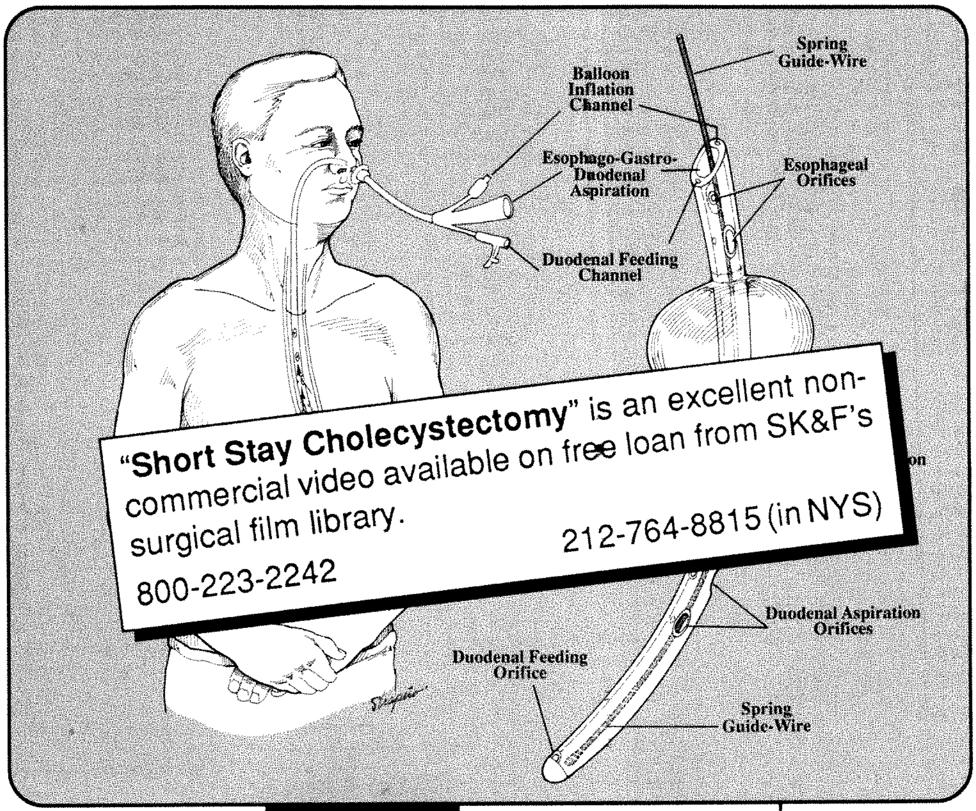

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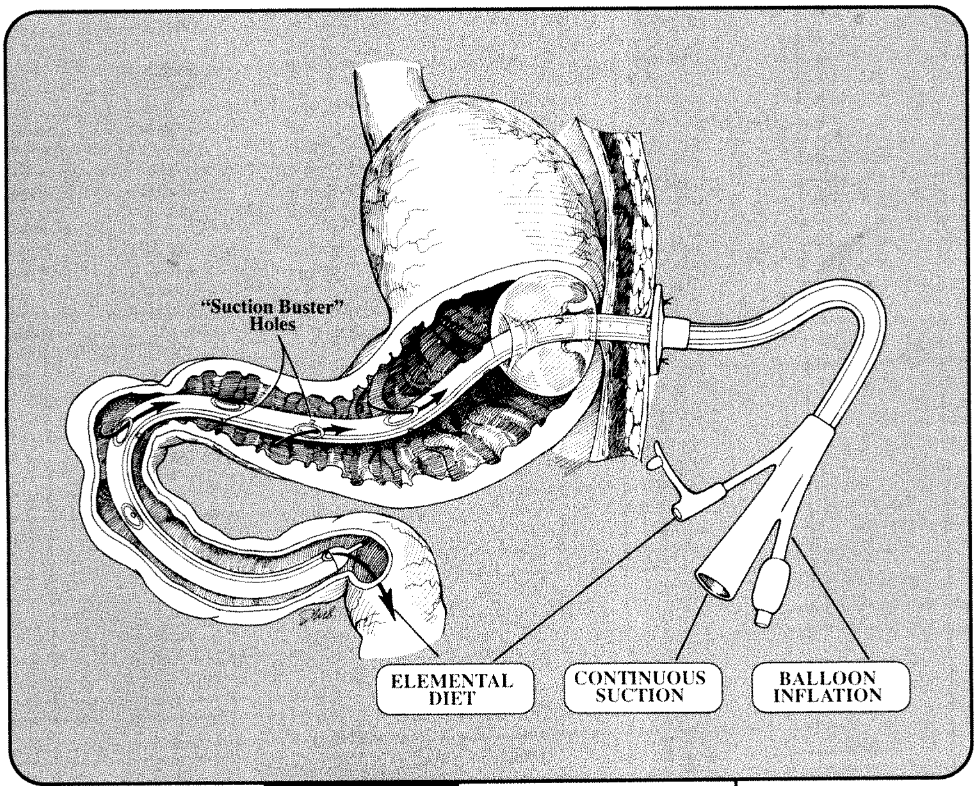

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CASE # 24 **AGE:** 55 **SEX:** FEMALE

DIAGNOSIS: CECAL CARCINOMA

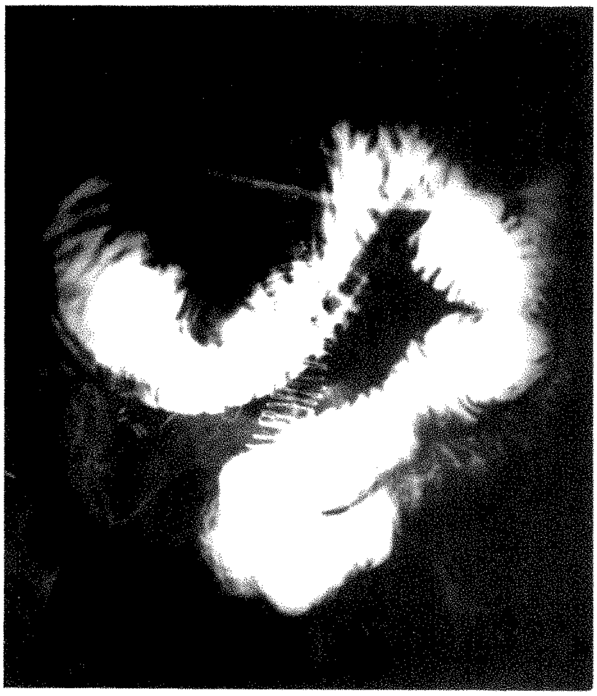
SYMPTOMS: ANEMIA (Hg 6 gm/dl)

OPERATION: RIGHT HEMICOLECTOMY & GASTROSTOMY

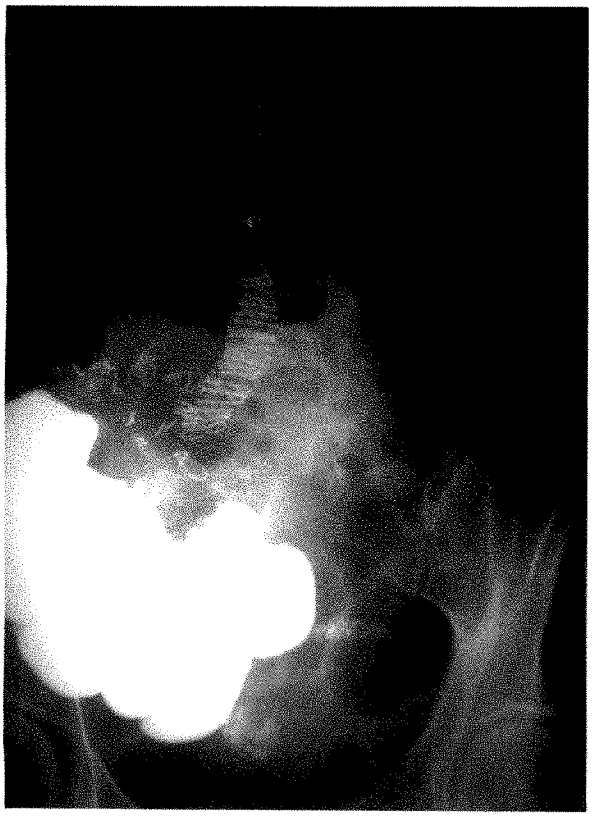
The patient had a right hemicolectomy with stapled (U.S. Surgical Corp) anastomosis and fascia closure and a MOSS® gastrostomy tube. The stomach and proximal duodenum were aspirated, with immediate simultaneous feeding into the distal duodenum.

Barium feeding 5 hours postop documented adequate motility. The deliberate excess was totally removed. No contrast (i.e.: excess feeding) escaped efficient aspiration within the proximal duodenum, to reflux into the stomach. (Figure A) Serial motility study showed barium had traversed the anastomosis and colon, and already was exiting in a spontaneous bowel movement by 21 hours postop. (Figure C)

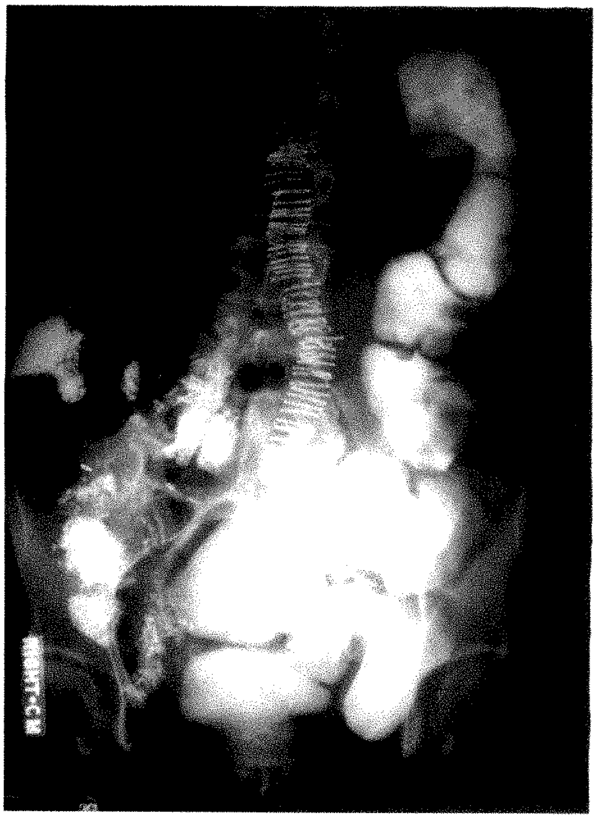
She received 300 ml/hr of Vivonex TEN (Norwich Eaton Pharm), absorbed 5,000 kcal the initial 20 hours, and then tolerated a general diet. She was the 4th patient discharged uneventfully 24 hours after bowel resection and reanastomosis.



A. Study @ 5 minutes (5 hours postop).
Note efficient removal of all excess barium, with none reaching the stomach.



B. Motility @ 4 hours (9 hours postop).
All barium is within the ileum.



C. Motility @ 16 hours (21 hours postop).
Barium is exiting in a spontaneous bowel movement.

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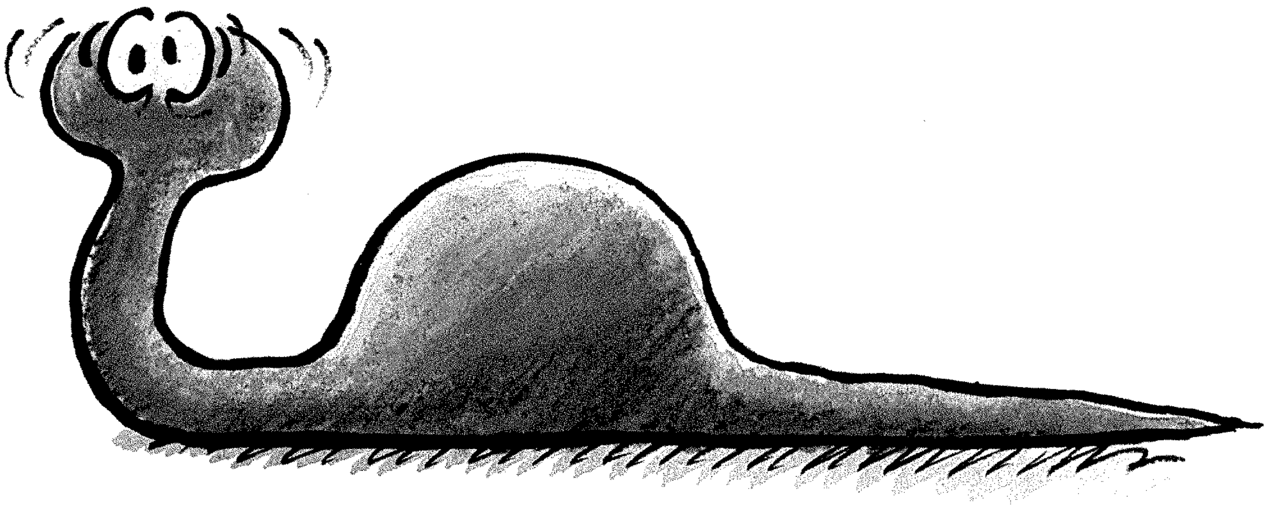

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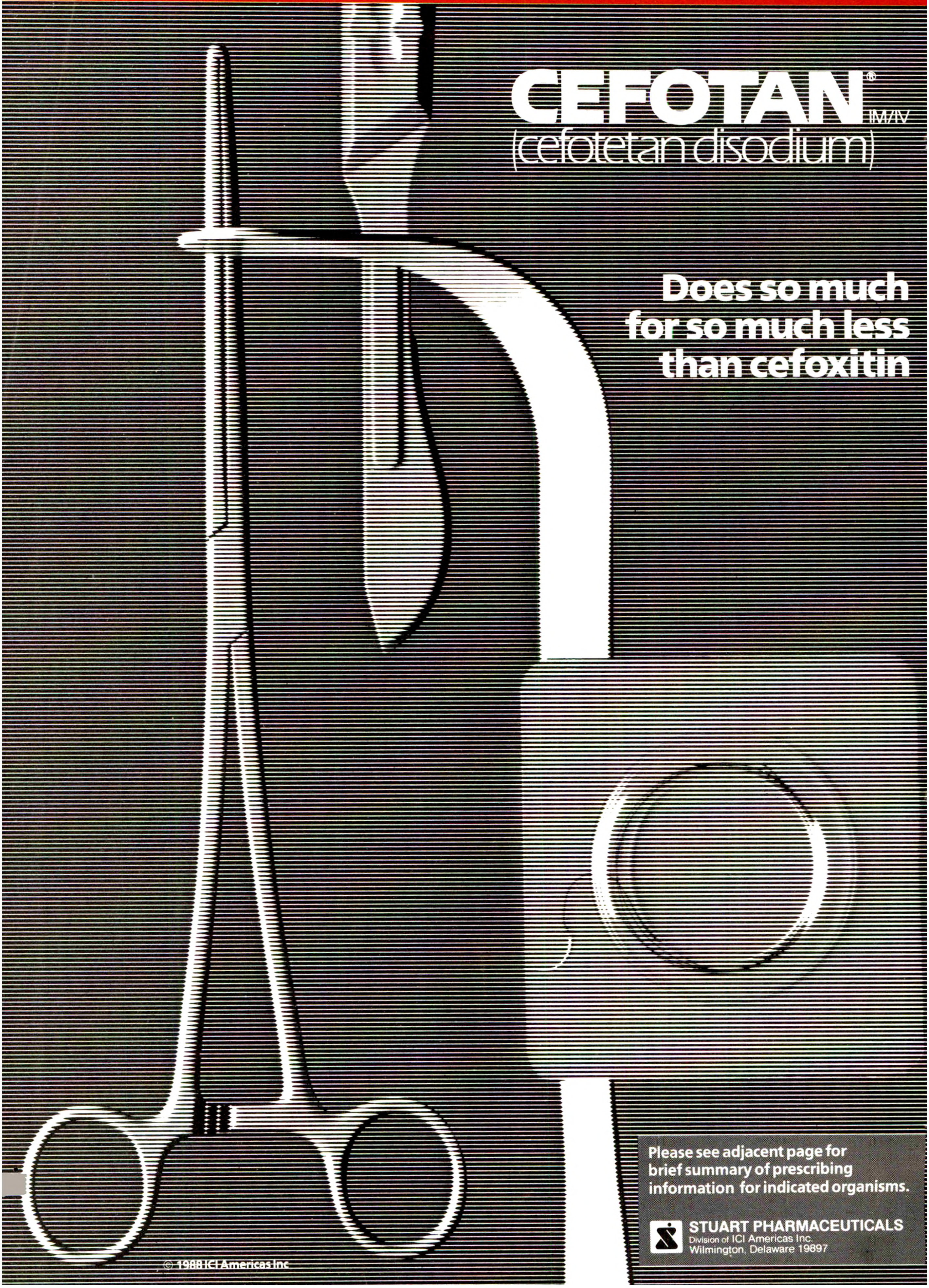

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For Intravenous or Intramuscular Use
BRIEF SUMMARY

INDICATIONS AND USAGE

TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary tract infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris*, *Providencia rettgeri*, and *Morganella morganii*).

Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.

Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.

Gynecologic infections caused by *Staphylococcus aureus*† (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus* species (excluding enterococci), *E coli*, *Proteus mirabilis*, *Neisseria gonorrhoeae*, *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*), *Fusobacterium* species,† and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species†).

Intra-abdominal infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*†), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*).

Bone and joint infections caused by *Staphylococcus aureus*.†

***NOTE:** Some strains of *Staphylococcus epidermidis* are resistant to cefotetan.

† Efficacy for this organism in this organ system was studied in fewer than ten infections.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.

PRECAUTIONS

GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state. Prothrombin times should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels of Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approx 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approx 2-4 times the usual human dose), only 1 of 10 treated animals was affected, and the degree of degeneration was mild. Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

CEFOTAN® (cefotetan disodium)

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In clinical studies the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5 percent of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4 percent of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2 percent of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2 percent of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than one percent of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

DOSAGE AND ADMINISTRATION

TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dose*	Every 12 hours
10-30	Usual Recommended Dose*	Every 24 hours
<10	Usual Recommended Dose*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED

CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

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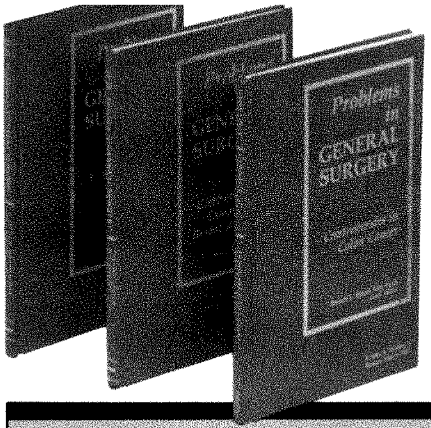

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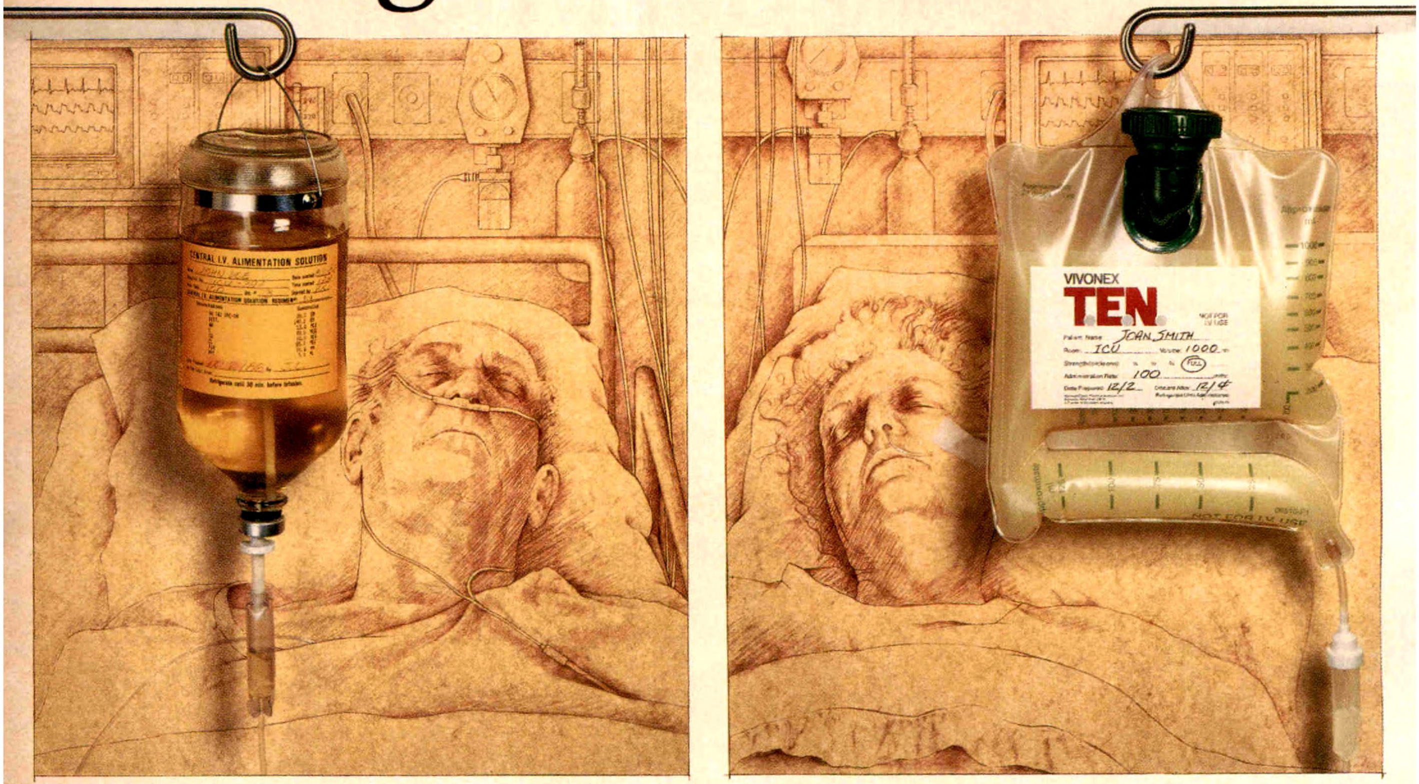

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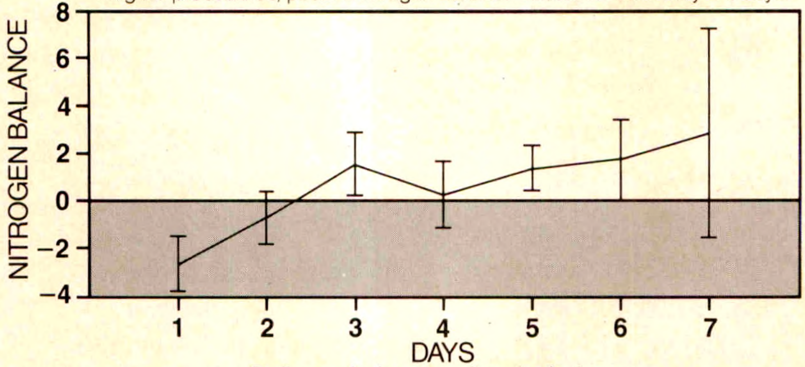

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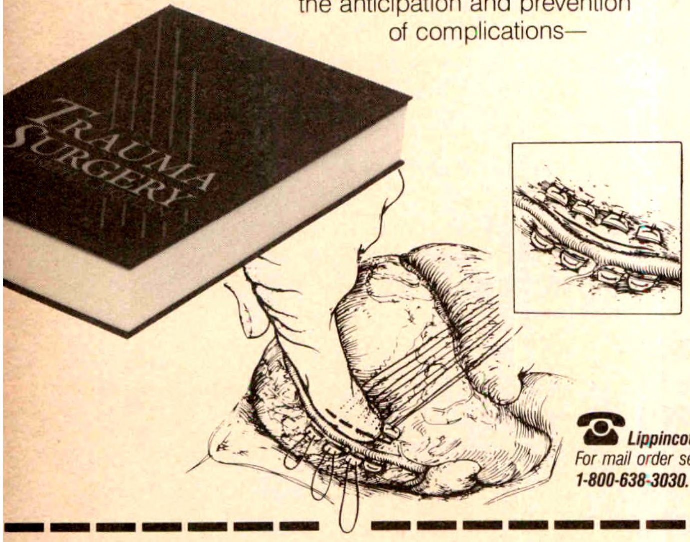

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ARNING
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ECAUTIONS
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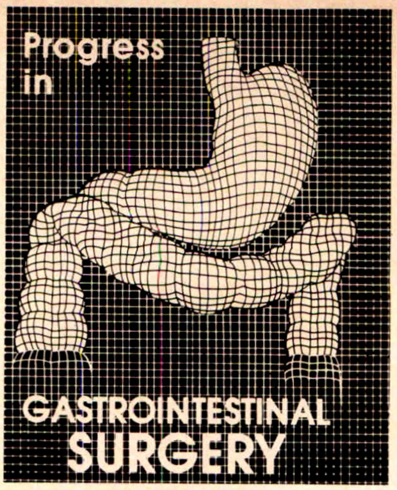

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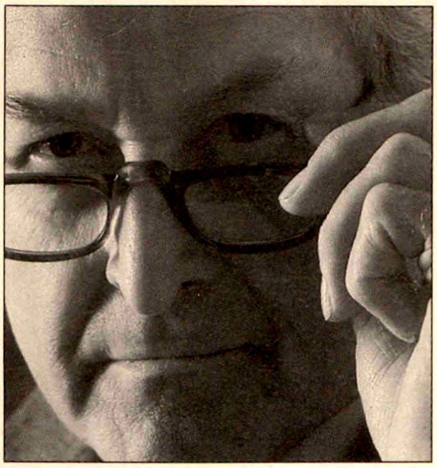
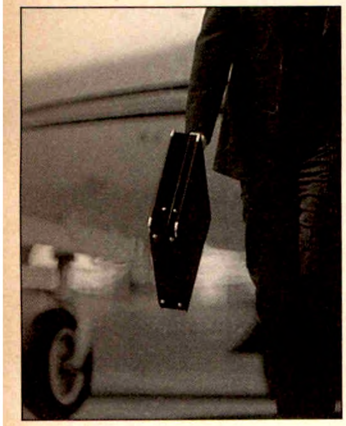
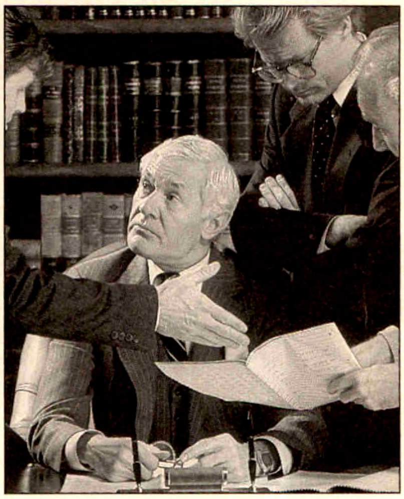
Do you really think he's going to sit still for a sitz bath?







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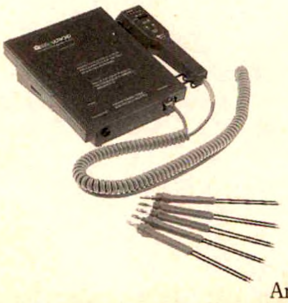

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[1] National Center for Health Statistics for 1985.

[2] A complete list of clinical evaluators is available upon request.

March 1988
Volume 207, Number 3

Annals of Surgery

Intraoperative Colonoscopy

JEFFREY L. COHEN, M.D., and KENNETH A. FORDE, M.D.

From the Department of Surgery, College of Physicians and Surgeons, Columbia University, and Presbyterian Hospital, New York, New York

From 1973 to 1985, we performed intraoperative colonoscopy on 68 patients with indications as follows: location of a previous polypectomy site (44%), inability to complete colonoscopy preoperatively (24%), locating nonpalpable polyps (13%), to define the source of lower gastrointestinal bleeding (4%), and to perform polypectomy (3%). Endoscopic evaluation influenced the outcome in 93% of the patients. There were two complications, both splenic capsular tears. Despite our increased ability to resolve several of the earlier indications for intraoperative colonoscopy by examination prior to celiotomy, there remains a significant role for intraoperative colonoscopy.

ENDOSCOPIC EXAMINATION of the colon is usually performed outside of the operating room. There are, however, occasional problems that may require intraoperative colonoscopy for successful surgical management. We have reviewed our experience with intraoperative colonoscopy in 68 patients during the period 1973–1985. During this time there has been a radical change in the attitudes of surgeons and gastroenterologists toward the role of flexible colonoscopy in the diagnosis and treatment of colonic disorders. Furthermore, the continued advancement in the quality of the instrumentation, as well as the enhanced skill of the endoscopist, has led to a redefinition of the indications for intraoperative colonoscopy. The changing experience is reflected in this report.

Materials and Methods

In the time period represented by this study, 4271 colonoscopic examinations have been performed by the Surgical Endoscopy Service of Columbia-Presbyterian Medical Center. The 68 intraoperative examinations represent, therefore, 1.6% of the total number of colonoscopies performed. Excluded from this analysis were patients who underwent total gastrointestinal tract endoscopy for chronic or recurrent bleeding of obscure origin. The colonoscopes employed for the examinations were those made by American Cystoscope Makers (ACM, Stamford, CT), Fujinon (Wayne, NJ), Olympus (Olympus Corp., New Hyde Park, NY), and Pentax (Orangeburg, NY).

Our technique for the performance of intraoperative colonoscopy has been described in detail.[1-3] After positioning the patient on the operating table with the thighs elevated by a couple of pillows, the tip of the colonoscope is gently inserted into the rectum and the instrument is then secured to the operating table. This posi-

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Reprint requests: Kenneth A. Forde, M.D., Department of Surgery, College of Physicians and Surgeons of Columbia University, 630 West 168th Street, New York, NY 10032.

Submitted for publication: July 15, 1987.

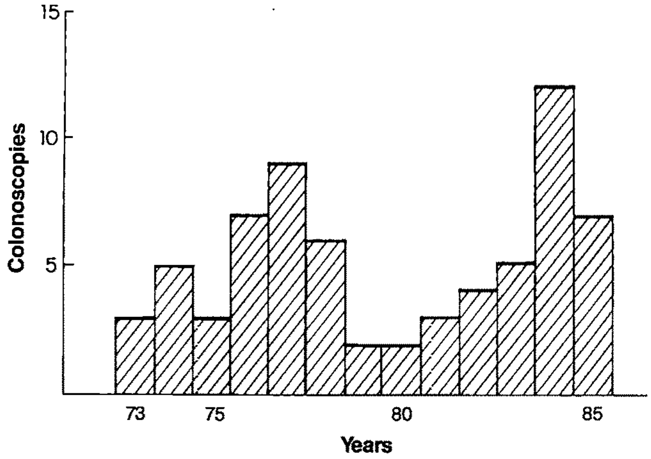

FIG. 1. Yearly incidence of intraoperative colonoscopy.

tioning allows adequate room for subsequent manipulation of the instrument. At celiotomy, the terminal ileum is occluded with a noncrushing clamp to prevent distention of the small intestine during the air insufflation necessary during passage of the colonoscope. With the aid and guidance of the operating surgeon, the endoscopist advances the instrument to the cecum. Lesions detected endoscopically can be marked with serosal sutures by the operating team.

Results

The yearly incidence of the performance of intraoperative colonoscopy is depicted in Figure 1. The biphasic nature of the experience is evident.

The overall indications for intraoperative colonoscopy for the entire time period of 1973–1985 are listed in Table 1.

Endoscopic evaluation of the colon at the time of operation was successful and influenced the outcome in 63 of the 68 patients (93%) in whom it was employed. Of the five failures, two were in the setting of active lower gastrointestinal bleeding, where the bleeding site could not be identified. The other three failures were technical inability to pass the colonoscope, inability to identify a polypectomy site, and inability to identify a colovesical fistula in one patient each.

TABLE 1. *Indications for Intraoperative Colonoscopy (N = 68)*

Indication	Number (%)
Location of previous polypectomy site	32 (44%)
Inability to complete colonoscopy preoperatively	16 (24%)
Location of nonpalpable polyps to define the limits of resection	9 (13%)
To define the source of GI bleeding	3 (4%)
To rule out synchronous lesions	3 (4%)
Polypectomy to limit the extent of resection	2 (3%)
Other	3 (4%)

The overall complication rate directly related to the procedure was 3%; both patients incurred splenic capsular tears, one of whom required a splenectomy.

Discussion

Over the last decade there has been a rapid expansion in the use of the flexible fiberoptic endoscope. This modality has become an essential tool in the surgeon's armamentarium. With the increased popularity of the endoscope, its uses have been limited only by the endoscopist's imagination. A natural extension of this technique by the surgical endoscopist has been in the operating room. Since the early 1970s, endoscopists have published sporadic reports of intraoperative colonoscopy and its possible indications.[3–6]

In our own early experience,[1] intraoperative colonoscopy yielded some degree of benefit in 27 of the 29 patients in whom it was employed. It should be pointed out, however, that several of these patients could have undergone preoperative colonoscopy had the endoscopist been involved earlier in the management of the patient. For this reason, as well as our increasing expertise in the use of the colonoscope, we believed that the need for intraoperative colonoscopy would decrease over time. It was therefore surprising that in reviewing the yearly incidence of intraoperative colonoscopies, an increase was seen over the past several years (Fig. 1). Intraoperative colonoscopy again comprised approximately 2% of our total yearly colonoscopic examinations. The reason for this later increased usage is to be found in the current indications.

When the indications are broken down into separate time segments representing the *early* and the *recent* period (Table 2), several trends are identified. If we look at the most frequent indications in both groups, the striking difference is that location of a previous polypectomy site has become the most frequent indication. That category alone represented 70% of the indications for intraoperative colonoscopy since 1970, as compared to the 25% for 1973–1979. This obviously reflects the changing orientation of both the medical and surgical communities toward the evaluation of gastrointestinal disease, with many more patients having undergone colonoscopic polypectomy prior to being seen by the surgeon. Despite reports by Ponsky and King[7] and Poulard et al.[8] there have been no articles documenting commonly employed methods of marking polypectomy sites at the time of their initial excision or subsequent preoperative colonoscopy. Repeating the colonoscopic examination prior to, rather than at the time of, operation may not be as rewarding in terms of localizing a polypectomy site to various parts of especially the sigmoid colon or in relation to the peritoneal reflection. These are areas of the colon where precise localization would be of great benefit to the surgeon, and even the use of fluoroscopy in the endoscopy suite if it is available may not be of universal accuracy.

As for the time limitation involved in the ability to visualize a polypectomy site, there was only one failure in our 32 attempts at identifying the site. This occurred in a patient whose intraoperative colonoscopy was performed eight days after polypectomy at another institution. Of the other 31 patients who were colonoscoped for this indication, the time delay ranged from 2 days to 8 weeks. While the findings at the polypectomy site can be quite variable, including ulceration, granulation tissue, or residual tumor, it can be expected from our experience that some evidence of a previous polypectomy may be demonstrable up to 6–8 weeks following initial colonoscopy.

Other less impressive but still important trends that were identified when comparing the early *versus* recent experiences was in the indications of inability to successfully colonoscope the patient preoperatively and for finding the source of gastrointestinal bleeding. There were significantly fewer patients since 1980 whom we were unable to colonoscope successfully in the endoscope suite. The four patients who underwent intraoperative colonoscopy since 1980 for this indication all had lesions visualized on barium enema which could not be seen by preoperative colonoscopy either secondary to adhesions or because of synchronous lesions. While the frequency of this indication is always somewhat dependent on referral patterns and the types of patients seen in one's practice, its incidence should continue to decrease as the experience of the endoscopist increases and the quality of the instruments improves.

Since 1980 we have not performed intraoperative colonoscopy for acute bleeding because this examination is much more successfully accomplished in the endoscopy suite, provided that the patient is hemodynamically stable. Two of our intraoperative failures were due to inability to identify sources of gastrointestinal bleeding. The ability to turn the patient and maneuver the colonoscope is quite inhibited by the patient's rigid positioning on the operating table. Ideally, all the resources of the endoscopist should be available in order to overcome the handicap of a colon filled with blood.[9] However, the technique of intraoperative endoscopic examination for acute bleeding remains an option for the endoscopist and surgeon.

Two patients on our service suffered complications as a direct result of intraoperative colonoscopy. Both complications were splenic capsular lacerations, one of which resulted in a splenectomy in addition to a colonic resection. In neither case was the colonoscopic examination especially difficult. It is possible that the intraoperative nature of the examination may have led to a false sense of security by the endoscopist. Bowden[10] similarly reported incurring one splenic hilar tear among 51 intraoperative endoscopies, although his occurred as a result of overdistention of the stomach from peroral introduction of the endoscope. Other complications not encountered in this study but reported on by others include prolonged ileus[10] and serosal laceration.[11] Most of the potential complications of intraoperative colonoscopy can be minimized by teamwork between the surgeons and the endoscopist as well as attention to detail during the procedure.

In conclusion, while the role of intraoperative colonoscopy has certainly undergone changes over the last decade, there are situations in which it provides a useful adjunct to the traditional methods of diagnosis and treatment of colonic diseases.

TABLE 2. *Indications for Intraoperative Colonoscopy (Early vs. Recent Periods)*

Indication	Early Period 1973–1979 (N = 35)	Recent Period 1980–1985 (N = 33)
Location of previous polypectomy site	9 (26%)	23 (70%)
Inability to complete colonoscopy preoperatively	12 (34%)	4 (12%)
Location of nonpalpable polyps to define the limits of resection	6 (17%)	3 (9%)
To define source of GI bleeding	3 (9%)	0 (0%)
Other	5 (14%)	3 (9%)

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Villous Tumors of the Duodenum

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Records of 32 patients with 34 villous and tubulovillous adenomas of the duodenum, treated at the Cleveland Clinic over the past 21 years, were reviewed. Twenty-two patients (69%) had complete resection of the adenoma; the incidence of malignancy was 47%. Five patients underwent a Whipple procedure; 4 patients had segmental resection of the duodenum; 12 had wide local excision of the adenoma; 1 had both a segmental resection and a local excision for two separate adenomas; and 5 patients had endoscopic excision alone. The remaining five patients underwent exploratory laparotomy alone or with palliative bypass procedures. A 28% recurrence rate was observed, all of these after segmental resection, local excision, or endoscopic excision. The highest recurrence rate was associated with local excision. The 2- and 5-year survival rates for patients with adenomas containing invasive cancer were 22% and 0%, respectively, compared to 87% and 87%, respectively, for benign adenomas (including those with carcinoma in situ). Twenty-two per cent of patients had intestinal polyposis syndromes. Duodenal adenomas were diagnosed a mean of 17 years after colectomy for polyposis, indicating the need for continued surveillance in these patients.

VILLOUS AND TUBULOVILLOUS ADENOMAS of the duodenum appear to behave in a manner similar to villous and tubulovillous adenomas of the colon and rectum, having both a high rate of recurrence after local treatment and a high incidence of malignancy. Villous and tubulovillous adenomas of the duodenum have been reported with increasing frequency over the last 15 years, probably because of the increasing use of upper gastrointestinal endoscopy for evaluation of patients with gastrointestinal complaints and for screening examination of patients with polyposis syndromes. Although the Whipple procedure remains the procedure of choice in treating adenomas containing invasive cancer, the selection of an appropriate procedure to treat benign villous and tubulovillous adenomas of the duodenum, especially those with carcinoma in situ, is controversial.

The purpose of this report is to review the Cleveland Clinic experience in treating 32 patients with villous and tubulovillous adenomas of the duodenum during the past 21 years and to determine the frequency of malignant change in these neoplasms, recurrence rates, and the effect of types of treatment on recurrence.

Patient Materials and Methods

The records of the Department of Pathology and the Department of General Surgery of the Cleveland Clinic Foundation from 1965 to 1986 were reviewed for all patients with villous and tubulovillous adenomas of the duodenum. Thirty-two patients with 34 adenomas were identified. Patient charts were reviewed, and data regarding adenoma size, location in the duodenum, type of surgery, pathology, and recurrence were analyzed. Lesions were classified as supra-ampullary, peri-ampullary, or infra-ampullary, depending on their location with respect to the ampulla of Vater. Only cases in which the adenoma was stated to arise from duodenal mucosa and had a significant villous component were accepted for this review. Statistical comparisons were made using Fisher's exact test and survival rates calculated using the life table method.[1]

The male:female ratio was 1:1, with a mean patient age of 60 years (range: 29–81 years). The most frequent presenting symptoms are given in Table 1. Other symptoms included diarrhea, anemia, fatigue, fever (second-

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ary to cholangitis from biliary obstruction), and recurrent episodes of pancreatitis.

The diagnostic procedures most frequently used were esophagogastroduodenoscopy, endoscopic retrograde cholangiopancreatography, barium swallow, CT scan of the abdomen, and percutaneous transhepatic cholangiography. In the remaining patients, diagnosis was made at operation, frequently after the patient had been referred from another hospital where cholecystectomy and common bile duct exploration had been performed without relief of symptoms.

The mean adenoma diameter was 3.7 cm with a range of 0.9–9 cm. Twenty-eight patients had only one duodenal adenoma. Four patients, all with familial polyposis, had more than one adenoma; one had a synchronous tubular adenoma near the ampulla of Vater and many fundic gland polyps in the stomach, another had two adenomas in the second portion of the duodenum, and a third (with Peutz-Jeghers syndrome) had a hamartoma of the third portion of the duodenum in addition to a villous adenoma. The fourth patient developed a second villous adenoma of the duodenum at a different site 4 years after prior treatment of an adenoma by segmental resection.

Eighty-eight per cent of the adenomas were located in the second portion of the duodenum. Most of these lesions were peri-ampullary. Two adenomas were in the first part and another two were in the third part of the duodenum.

A biopsy was obtained before operation in 24 patients. In 23 patients, this was performed at the time of upper gastrointestinal endoscopy, and in one patient at the time of a previous laparotomy in another hospital. Brush cytology was obtained in ten patients. Biopsy correlated with the final pathology in 17 patients (71%) but was falsely negative for adenocarcinoma in six (25%). There were no false-positives. In four patients (40%) cytology was falsely negative for adenocarcinoma. Final examination of post-treatment specimens revealed 19 benign adenomas, three of which contained carcinoma in situ. Invasive adenocarcinoma was present in 15 lesions.

Twenty-seven patients were treated by operation, and five patients had endoscopic polypectomy, either by snare or laser excision. The patients were operated on by five surgeons; the majority of procedures were performed by one surgeon (R.E.H.).

A Whipple procedure was performed in five patients. The ampulla was resected and required reconstruction in one of five patients undergoing segmental resection of the duodenum. Common bile duct and pancreatic duct-duodenal reconstruction was performed in 7 of 13 patients who underwent wide local excision of a periampullary adenoma.

TABLE 1. *Presenting Symptoms*

	No. of Patients	%
Jaundice	13	41
Weight loss	13	41
Epigastric pain	12	38
Melena/guaiac + stool	5	16
Partial intestinal obstruction	3	9
Asymptomatic	3	9

In two patients, unresectable carcinoma was present and choledochojejunostomy or choledochoduodenostomy performed. In three other patients, liver metastases were present; exploratory laparotomy only was performed in one patient and choledochojejunostomy in the other two.

Five patients underwent endoscopic removal of six adenomas. Three adenomas were removed by conventional snare excision and three by laser excision. Adenomas removed using the laser required two, two, and five laser sessions, respectively, until the lesions were completely removed. In one case, a biliary stent had to be inserted prior to adenoma excision in order to avoid ductal injury.

The mean adenoma size of patients undergoing local excision was 2.7 cm, 5.6 cm for segmental duodenal resection, and 4.4 cm (all malignant) for those having a Whipple procedure. No description of size was available for four of the six adenomas removed endoscopically.

Results

The mean hospital stay was 17.3 days, with a range of 3–39 days. One patient was treated endoscopically as an outpatient. The other four patients treated endoscopically were hospitalized a mean of 5.3 days (range: 3–8 days).

The overall hospital mortality rate was 3.5% (one death) with a postoperative morbidity of 56%. None of the patients undergoing a Whipple procedure died, but postoperative complications occurred in two of five patients (40%). One of the five patients who had segmental duodenal resection died postoperatively of acute hemorrhagic pancreatitis, the only death in this series. All five patients in this group had postoperative complications. Duodenotomy and wide local excision of the tumor had no mortality rates, but 62% of patients had postoperative complications. The only complication occurring in six endoscopic polypectomies was a 3 g/dL drop in hemoglobin in one patient, requiring admission for observation but no transfusion.

The complications that occurred in the group as a whole included postoperative bleeding requiring transfusion in seven patients, temporary duodenal fistula in three patients, and pancreatitis in two patients.

TABLE 2. *Local Recurrence by Primary Procedure*

	No. of Patients	%
Local excision	6/13	46
Endoscopic excision	2/6	33
Segmental resection	1/5	20

Invasive adenocarcinoma was present in 15 patients (47%). The most frequent site of involvement for both adenomas with and without malignant change was the periampullary duodenum. A dilated common bile duct did not always indicate malignancy; 86% of patients with cancer had a dilated common bile duct, but, conversely, only 63% of patients with a dilated bile duct had cancer. Size was also not an accurate predictor of adenocarcinoma ($p = 0.202$).

Villous and tubulovillous adenomas containing adenocarcinoma were treated by a Whipple procedure in five patients, segmental duodenal resection in two, wide local excision in three, and exploratory laparotomy with or without bypass in five patients. Of the 15 patients with adenocarcinoma, 6 are alive without evidence of cancer, 1 is alive with cancer, and 8 have died of carcinoma. The mean follow-up time for these patients was 16 months (range: 1–60 months).

Carcinoma in situ was present in three adenomas and severe dysplasia was found in another two. Four of these five adenomas were treated by local excision and one by segmental duodenal resection. The only recurrence in this group occurred after local excision of a 3-cm villous adenoma with carcinoma in situ, with positive margins of resection in the pancreatic duct. Recurrence was detected at 8 months and was treated by endoscopic biopsy (excision) revealing the presence of a recurrent adenoma with severe dysplasia. This patient is currently being followed by endoscopic examination and biopsies at 6-month intervals. None of the other patients with carcinoma in situ or severe dysplasia developed a recurrence.

TABLE 3. *Patient Follow-up*

	No. of Patients
Alive without evidence of adenoma	15
Alive with recurrent adenoma	3
Alive with invasive adenocarcinoma	1
Dead of adenocarcinoma	10
Dead of other causes*	2
Dead of unknown cause	1
Total	32

* Includes one death on postoperative day 3 secondary to hemorrhagic pancreatitis.

TABLE 4. *Survival Rates*

	1 Year (%)	2 Year (%)	5 Year (%)
Patients with benign adenomas	94	87	87
Patients with invasive cancer	73	22	0
All patients	85	72	43

Recurrent adenomas have been diagnosed in 9 of 32 patients (28%), a mean of 12 months after operation or endoscopy (range of from 1 to 54 months). Six of these nine recurrences occurred after local excision, two after endoscopic laser excision, and one after segmental duodenal resection (Table 2). In those patients with recurrence, the initial adenoma was benign in six of nine patients. Two patients with recurrences after treatment of benign adenomas had adenocarcinoma in the recurrent lesion. Choledochoduodenostomy was performed in these two patients; all other patients with a recurrence underwent resection or endoscopic removal. Three patients died 29–69 months after diagnosis of the recurrent lesion, two of cancer and the other of unknown causes. Six patients are alive 6–19 months (mean 12 months) after treatment of recurrent benign lesions.

Sixty-two per cent of the patients have been followed for more than 1 year postoperatively. The mean time of follow-up is 22 months; however, 25% of patients have been treated less than 18 months prior to completion of this study. Table 3 lists patient status at follow-up. Survival rates, calculated using the life table method, are shown in Table 4 and Figure 1.

Seven of these 32 patients (22%) with villous or tubulovillous adenomas of the duodenum had an intestinal polyposis syndrome: six patients had familial polyposis coli and one patient had Peutz-Jeghers syndrome. The mean age in this subgroup of patients was 49 years, 12 years younger than the mean age of our patients without a polyposis syndrome. The mean adenoma diameter in this group was 4 cm, similar to that of the other patients. Patients with polyposis syndromes were the only patients with a history of previous polyps, all of these having been in the colon. Five patients had previously been treated by total proctocolectomy and end ileostomy, one patient by a subtotal colectomy and ileorectal anastomosis, and one patient (with Peutz-Jeghers) had undergone a partial colectomy. These procedures had been performed 2–32 years (mean: 17 years) prior to identification of the duodenal adenomas. Duodenal adenomas were diagnosed 14–33 years (mean: 24 years) after diagnosis of the polyposis syndrome. Two of these duodenal lesions were asymptomatic and were diagnosed on surveillance endoscopy. Adenocarcinoma was present in the villous adenoma in two of seven patients. In one patient, at operation metastatic disease was already present and a biliary-intestinal bypass was performed; in the other patient a Whipple procedure was performed, but the patient died of metastatic disease 13 months later. One patient had two benign villous adenomas of the duodenum occurring 4 years apart. The first was treated by segmental resection and the second by local excision. The remaining adenomas were all benign and were treated by endoscopic snare or laser excision. Follow-up studies have shown that two of the patients with polyposis syndromes developed new adenomas at sites other than those from which polyps had previously been removed at 20 and 36 months. Both of these were asymptomatic and were noted on routine surveillance endoscopy and removed endoscopically.

Discussion

Duodenal villous adenomas tend to be large lesions. In a previous review, 22 of 23 villous adenomas were greater than 3 cm in diameter[2]; this concurs with the mean adenoma diameter of 3.7 cm in this series. Although the incidence of adenocarcinoma in colorectal villous adenomas increases with increasing adenoma size, Kutin et al. found that this is not true for villous adenomas of the duodenum.[3,4] Our data support this view.

A 25–50% rate of cancer in villous adenomas of the duodenum has been reported.[3,5–8] In our series, the incidence of malignancy was 47% and the resectability rate was 64%. We concur with the opinion of others who have recommended that all villous adenomas of the duodenum be considered potentially malignant until proven otherwise.[9]

Pancreatoduodenal resection (Whipple) remains the operation of choice for patients with invasive periampullary carcinoma. Small lesions not adjacent to the ampulla of Vater and lesions with foci of carcinoma in situ may be treated by segmental duodenal resection or by wide local excision. Because of the magnitude of the Whipple procedure and its potential morbidity and mortality rates, we believe that this procedure is justified only in patients with invasive adenocarcinoma. Due to the small number of patients, no meaningful statement can be made regarding survival after pancreatoduodenectomy for villous adenomas with invasive malignancy. A recent review of patients with periampullary carcinoma treated by pancreatoduodenectomy at the Cleveland Clinic did, however, demonstrate that patients with papillary adenocarcinoma had a 5-year survival rate of 49% compared to 18% for patients with nonpapillary tumors.[10]

We have not observed a tendency for benign lesions to extend up the biliary or pancreatic ducts. At this time, we cannot recommend a Whipple procedure for benign lesions or for those with carcinoma in situ, as has been recommended by Ryan et al.[11]

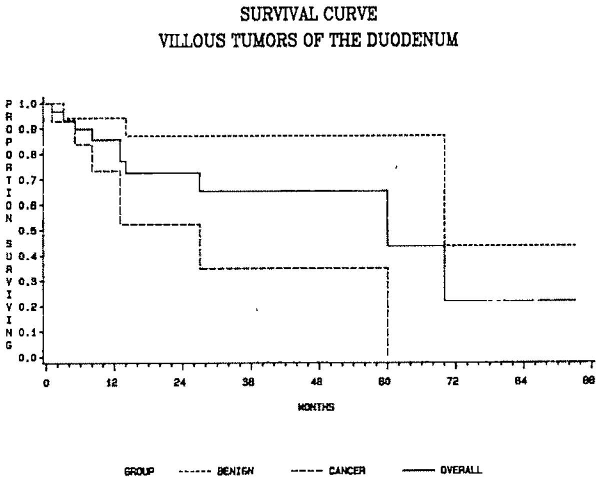

FIG. 1. Survival curves for all patients, for those with benign adenomas, and patients with adenomas containing invasive adenocarcinoma.

Our present recommendation for treatment is shown in Figure 2. It is based on examination of an excisional or endoscopic biopsy of the entire tumor since random biopsies are not reliable in detecting invasive adenocarcinoma. Endoscopic excision alone may be adequate treatment for benign lesions, but may be limited by the proximity of the biliary and pancreatic ducts. The ability to place biliary stents and perform sphincterotomies endoscopically has increased the number of lesions that can be treated this way, but more than one endoscopic treatment is frequently necessary. The use of a multipolar electrode (Bicap®, ACMI, American Cystoscope Manufacturer, Stamford, CT) or heater probe (Olympus) is preferred for ablation. A side-viewing endoscope is also essential for adequate visualization of the periampullary area. The rate of morbidity of endoscopic excision in this series was minimal, although hospitalization for observation was necessary in most patients.

Wide local excision involves removal of the lesion to the level of the submucosa and frequently requires operative reconstruction of the bile and pancreatic ducts to duodenal mucosa. Recurrence was common (6 of 13 patients) after local excision. The overall recurrence rate of 28% in our series was most likely related to the narrow margins obtained after a local resection because of the proximity of the bile and pancreatic ducts and the difficulty in determining clear margins because of the soft, friable nature of these adenomas. Continuing endoscopic surveillance at 6- to 12-month intervals permits the detection and treatment of recurrent lesions. The major danger lies in poor patient compliance. Two patients with benign lesions who did not return for periodic follow-up subsequently developed recurrent tumors with malignant change and died of cancer.

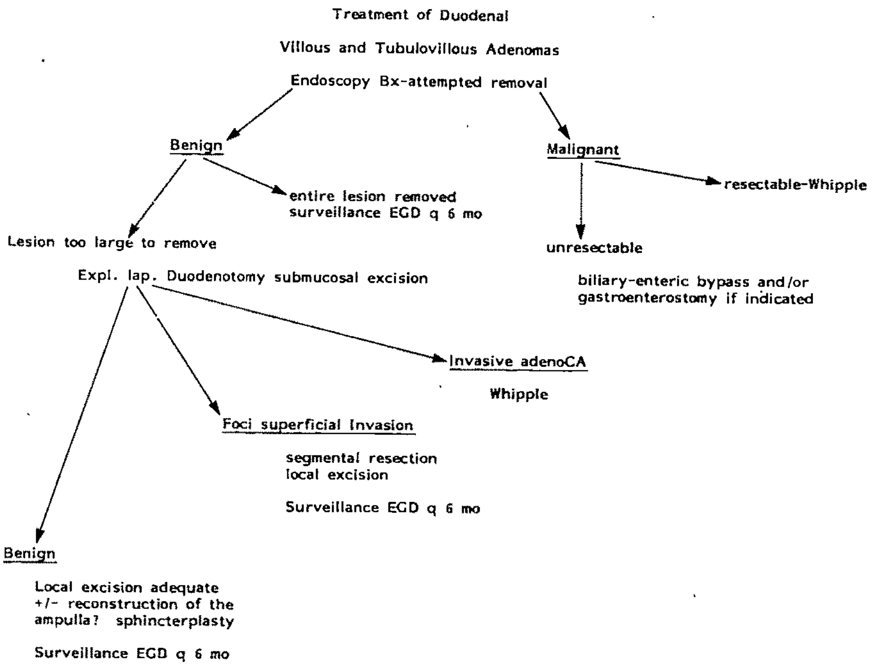

FIG. 2. Treatment strategy for duodenal adenomas.

Twenty-two per cent of our patients had intestinal polyposis syndromes. One patient in our series had Peutz-Jeghers syndrome. Although there are several reports of upper gastrointestinal malignancies in patients with Peutz-Jeghers syndrome, we are not aware of any reports of duodenal villous adenomas in these patients.[12–14]

Duodenal carcinoma is the most frequent extracolonic malignancy in patients with familial polyposis coli (FPC), reported in 2–12% of patients.[3,15,16] Prophylactic colectomy and ileorectal anastomosis or proctocolectomy have led to longer survival in these patients and have given them time to develop a periampullary carcinoma.[17,18] Many investigators believe that Gardner's syndrome represents a *pleiotropic manifestation* of a genetic defect with a predisposition of the entire gastrointestinal tract to develop polyps.[15,16,19–22] Fundic gland polyps have been reported in these patients, as well as a 41–100% incidence of synchronous duodenal polyps.[15–18,20,22–24] Polyps may easily be missed by barium swallow examination, while endoscopy permits direct vision and the ability to biopsy. In the majority of cases, the papilla has a nodular or granular yellow to white appearance, and the affected mucosa appears lighter than normal.[15,19,20] In some patients biopsies of normal appearing ampullae may disclose adenomatous changes.[23] For this reason, some investigators recommend routine biopsy in these patients.[24] Few papers on duodenal polyps in patients with FPC have reported on the types of adenomas present in these patients. The number of tubular adenomas in our FPC patients at the Cleveland Clinic has greatly exceeded the number of villous adenomas found. In a recent prospective study, only 21% of FPC patients with duodenal adenomas had tubulovillous or villous adenomas.[25]

The mean time interval from diagnosis of FPC to diagnosis of a periampullary tumor in our series was 24 years. In one report, the mean age of FPC patients without duodenal adenomas was 29 years; it was 34 years for patients with FPC and duodenal adenomas and 45 years for FPC patients with periampullary carcinoma, suggesting an adenoma-carcinoma sequence in the duodenum similar to that in the colon and rectum.[18,24]

Patients being evaluated for FPC should have a routine surveillance esophagogastroduodenoscopy (EGD). If negative, this procedure is repeated annually. If adenomas are found, they should be removed and endoscopic follow-up performed at 6-month intervals. The only patients in this series that developed subsequent new villous adenomas of the duodenum were polyposis patients. The mean 17-year delay between colectomy and diagnosis of the duodenal adenoma indicates that long-term follow-up of these patients is necessary.

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Hirschsprung's Disease

Identification of Risk Factors for Enterocolitis

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From 1975 to 1985, 80 infants and children were treated at a major pediatric hospital for Hirschsprung's disease, 19 (24%) of whom developed enterocolitis. In 9 neonates (18%) and 4 infants (29%) enterocolitis was present at diagnosis of Hirschsprung's disease, while 4 children acquired enterocolitis following a pull-through procedure. Significant risk factors for development of Hirschsprung's-associated enterocolitis (HAEC) were delay in diagnosis beyond 1 week of age and the presence of trisomy 21. HAEC did not occur more frequently in patients with long-segment aganglionosis, nor did an initial episode of HAEC confer a higher risk of recurrent enterocolitis. HAEC following a pull-through procedure was correlated with an anorectal stricture in three of four cases. Although neonates with HAEC had a low mortality rate (5%), their morbidity rate was 30% and their hospitalization was twice as long as neonates without enterocolitis.

Despite significant advances in the recognition, diagnosis, and operative management of Hirschsprung's disease, enterocolitis remains its major source of morbidity and mortality.[1] Historically, the incidence of Hirschsprung's-associated enterocolitis (HAEC) has approached 50% with a mortality rate of 30%.[2] In recent surveys of 2824 infants and children with Hirschsprung's disease in North America and Japan, HAEC occurred in nearly one fourth of patients, with a mortality rate between 6% and 30%.[3,4]

This study evaluates the occurrence of enterocolitis in 80 infants and children treated for Hirschsprung's disease during the last decade at a major pediatric center. Factors associated with the development of enterocolitis are identified and the medical and economic impact of HAEC is analyzed.

From the Division of Pediatric Surgery, the Department of Surgery, and the Department of Pathology, Ohio State University College of Medicine, and the Children's Hospital, Columbus, Ohio

Methods

The charts of all patients (80 infants and children) initially treated for Hirschsprung's disease at the Children's Hospital, Columbus, OH between 1975 and 1985 were reviewed. Factors evaluated were sex, age at diagnosis, level of aganglionosis, familial history of Hirschsprung's disease, presence of associated anomalies, signs of HAEC (fever, distention, diarrhea), symptoms of HAEC (prostration, lethargy, crampy abdominal pain), positive cultures (blood, stool, peritoneal), type of colostomy and pull-through procedure, development of HAEC in relation to operative treatment, complications of treatment for HAEC, length and cost of hospitalization, and mortality rate.

Diagnosis of HAEC was made on the clinical findings of abdominal distention, diarrhea, and temperature greater than 38 C.[5,6] Statistical analysis was done using either a paired or unpaired t-test, or chi square analysis. Statistical significance was given for $p < 0.05$.

Results

Total Group

The patients included 60 males (75%); a family history of Hirschsprung's disease was present in 3 (4.7%). Diagnosis of Hirschsprung's disease was made at 30 days of age or less in 51 patients (64%); 31–180 days in 14 (18%); and over 6 months in 15 (18%). The level of aganglionosis was confined to the distal rectum in 2 (2%); rectosigmoid in 66 (83%); transverse colon in 5 (6%); and total colon in 7 (9%).

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Trisomy 21 was present in 13 patients (16%). Ten children (77%) with trisomy 21 had other associated congenital anomalies including cardiac (6), central nervous system (1), and gastrointestinal (3). In the 67 patients without trisomy 21, associated congenital anomalies occurred in 16 (24%): cardiac (4), central nervous system (5), genitourinary (2), maxillofacial (3), and skeletal (2).

Initial operative procedures included sigmoid colostomy (60), transverse colostomy (5), ileostomy (8), anal myectomy (2), and cecostomy (1). Three children were treated with daily saline rectal washouts of whom two underwent a subsequent pull-through and one continues nonoperative management. Fifty-nine patients have undergone a definitive pull-through procedure: Duhamel (40); Swenson (10); Soave (7); and anal myectomy (2).

HAEC Group

Nineteen of the 80 patients developed at least one episode of HAEC, an incidence of 24%. The level of aganglionosis in patients with HAEC was confined to the rectosigmoid in 16 (85%), transverse colon in 1 (5%), and total colon in 2 (10%). Enterocolitis did not occur at a significantly more frequent rate in patients with longer levels of aganglionosis: 24% for rectosigmoid aganglionosis, 20% for transverse colon aganglionosis, and 29% for total colon aganglionosis.

Of the 19 patients with HAEC, 13 were neonates and infants whose presenting diagnostic sign of Hirschsprung's disease was enterocolitis. Two infants developed HAEC after decompressive enterostomies, while four children acquired enterocolitis after a pull-through procedure. Two of the 13 infants with HAEC at diagnosis developed recurrent enterocolitis (15%), one after colostomy and one after pull-through. Three of the four children with HAEC following a pull-through procedure had recurrences.

Six of the 19 patients with HAEC had trisomy 21 (32%), although trisomy 21 occurred in only 16% of the 80 patients in the total group with Hirschsprung's disease. A significantly ($p < 0.05$) larger proportion of patients with trisomy 21 developed HAEC compared to patients without trisomy 21 (Table 1).

The clinical signs and symptoms of HAEC were abdominal distention (19), diarrhea (19), and temperature greater than 38 C (16) (Table 2). Bloody stools occurred in four patients. Five children had positive blood cultures (27%): *Escherichia coli* (4) and *Enterobacter* and *E. coli* (1). *Bacteroides fragilis* and *E. coli* were cultured from one child's peritoneal fluid. Six patients had infections with enterocyte-adherent organisms based on tissue specimens and tissue assays: toxigenic *E. coli* (4), toxigenic *Clostridium difficile* (1), and *Cryptosporidium* (1).

TABLE 1. *Association of Trisomy 21 and Enterocolitis*

	Trisomy 21	Others
Total group (80)	13	67
Enterocolitis (19)	6	13
% with enterocolitis	46*	19

* $p < 0.05$.

TABLE 2. *Clinical Signs and Symptoms in 19 Patients with Enterocolitis*

Sign or Symptom	No. (%)
Abdominal distention	19 (100)
Diarrhea	19 (100)
Temperature > 38C	16 (84)
Bloody stools	4 (25)

HAEC in Neonates and Infants

Of the 13 patients with HAEC at diagnosis, 9 were neonates less than 30 days of age and 4 were infants between 1 and 6 months of age. The 9 neonates with HAEC at diagnosis represented 18% of the 51 neonates with Hirschsprung's disease in the total group. The mean age at diagnosis for the neonates with HAEC was 16.6 ± 11.3 d (mean ± SD), significantly later ($p < 0.01$) than the mean age at diagnosis of 4.6 ± 6.5 d for the neonates without enterocolitis. In addition, significantly more neonates presented with HAEC after 10 days of age as compared to neonates without enterocolitis (Fig. 1). The mean age for passage of meconium was 53 ± 12 h in the neonates with HAEC and 40 ± 4 h in neonates without HAEC, a significant difference at $p < 0.05$.

Seven of the 9 neonates with HAEC were considered to have a significant delay in diagnosis. In these patients

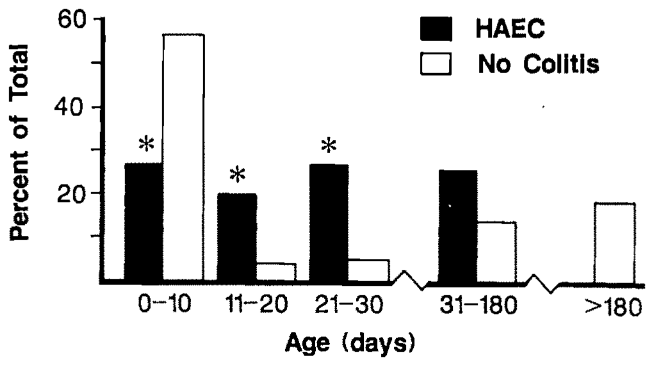

FIG. 1. Mean age at diagnosis of Hirschsprung's disease in days. Enterocolitis was present in significantly more neonates (*$p \leq 0.05$) diagnosed after 10 days of age.

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a history of abnormal or infrequent passage of stools followed by abdominal distention, lethargy, and diarrhea had occurred for 1 or 2 weeks prior to referral. Two neonates became acutely ill and were diagnosed promptly. The first, a 2-day-old, developed emesis and abdominal distention; at laparotomy he had enterocolitis and a cecal perforation. The second neonate, a 6-day-old with trisomy 21 and cardiac anomalies, was referred after 24 hours of foul-smelling diarrhea and lethargy.

Four infants (29%) presented with HAEC between 50 and 70 days of age. In three patients a history of severe constipation with abdominal distention was elicited. The fourth infant had multiple congenital anomalies including trisomy 21, cardiac disease, duodenal stenosis, and infralevator imperforate anus. Constipation persisted following a perineal anoplasty with the acute onset of abdominal distention and diarrhea.

Three neonates with HAEC developed complications before or after colostomy (30%). One infant sustained a cecal perforation secondary to severe colitis, which was not recognized at the initial operation for sigmoid colostomy. On the third postoperative day he developed an evisceration and required reexploration and ileostomy. One neonate sustained a perforation of the sigmoid colon during rectal saline washouts prior to colostomy. A third infant required revision of a sigmoid colostomy for retraction of the stoma.

Neonates with HAEC at diagnosis were hospitalized an average of 25 days compared to an average of 13 days for neonates without HAEC ($p < 0.05$). The average hospital cost for infants with HAEC ($17,810) was significantly greater ($p < 0.01$) than for infants without HAEC ($7,328).

Three infants with HAEC died, all of whom had trisomy 21. However, only one death was directly attributable to HAEC, a mortality rate of 5%. A 2-month-old infant had undergone a right transverse colostomy at 22 days of age for clinical HAEC. He recovered but returned 6 weeks later moribund with HAEC; autopsy confirmed diffuse enterocolitis and a perforation in the ascending colon 5 cm proximal to the colostomy. A second infant with an endocardial cushion defect who had presented with HAEC and recovered following sigmoid colostomy died from progressive cardiac failure. The third infant suffered a fatal aspiration pneumonia having recovered from HAEC.

HAEC Following Operative Procedures

Two infants developed enterocolitis following initial operation: colostomy in one and ileostomy in the other. The first patient was diagnosed at 24 hours of age with Hirschsprung's disease, trisomy 21, and an endocardial cushion defect; a sigmoid colostomy was performed. He returned at 1 month of age with HAEC and recovered without complication. Recurrent enterocolitis has not developed; definitive pull-through has been deferred because of severe cyanotic cardiac disease.

The second infant underwent an ileostomy for total colonic Hirschsprung's disease at 18 days of age. Eight months later he developed enterocolitis and recovered after prolonged total parenteral nutrition. This patient awaits a definitive pull-through procedure.

Five children acquired HAEC following a pull-through procedure, of whom four had no previous episodes. Three patients experienced two or more episodes of HAEC within 2 years of the pull-through. All children with post–pull-through HAEC were evaluated by barium enema, proctoscopy and sigmoidoscopy, colonic biopsy, or anal manometry. In three patients an anorectal stricture was diagnosed: one following a Swenson pull-through complicated by anastomotic leak, and two after uncomplicated Soave and Swenson procedures. All required secondary operations including anal dilatation (1) and internal sphincterotomy (2). A fourth child with severe psychomotor retardation developed multiple episodes of HAEC following an uncomplicated Duhamel pull-through and required an end-ileostomy for ultimate relief. A fifth patient with trisomy 21 developed *Cryptosporidiosis* enterocolitis 2 years after a Duhamel pull-through and recovered without further episodes.

Discussion

Prompt diagnosis of Hirschsprung's disease and expeditious placement of a decompressive enterostomy above the level of aganglionosis have been considered critical factors in the prevention of enterocolitis.[5] Although most pediatric surgical centers strictly adhere to these guidelines, HAEC continues to be a serious, often life-threatening condition. Our study underscores many accepted features of HAEC and, more importantly, identifies potential risk factors for its development.

HAEC has been characterized by an increased incidence and high mortality rate in the neonatal period. In 1962 Bill and Chapman[2] noted that neonates comprised 88% of patients with preoperative HAEC and accounted for all of the deaths. The 1975–1976 survey of 1196 infants and children by the Surgical Section of the American Academy of Pediatrics reported enterocolitis in 15% of patients at diagnosis of Hirschsprung's disease of whom one fourth were less than 3 months of age.[3] The Surgical Section survey concluded that the diagnosis of Hirschsprung's disease should be established by 1 month of age to reduce the incidence of enterocolitis.

In our series 51 of the 80 patients (64%) were diagnosed within the first month of life, yet HAEC occurred in 9 (18%) of the neonates. Closer evaluation discloses that the average age at diagnosis for neonates with HAEC was 16 days compared to 4 days for neonates without enterocolitis. Furthermore, three fourths of our patients with enterocolitis at diagnosis were less than 1 month of age. Clearly, patients in our series required diagnosis of Hirschsprung's disease early in the neonatal period, as soon as the first week of life, to decrease their risk of enterocolitis.

Three recent series confirm the importance of diagnosis in the early neonatal period. Grosfeld et al.[6] in 1978 reported 89 patients with Hirschsprung's disease of whom 34 (38%) were diagnosed under 1 month of age and 7 (20%) experienced neonatal enterocolitis. In Polley and Coran's 1986 series of 35 neonates with Hirschsprung's disease,[7] the average age at diagnosis was 9.9 days, yet the incidence of enterocolitis was 11%. Twenty-six neonatal cases of Hirschsprung's disease were reviewed by Klein et al.[8] in which diagnosis and decompressive enterostomy were accomplished by 2 weeks of age and no cases of HAEC were documented. Our data in conjunction with these reports substantiates the necessity of diagnosis of Hirschsprung's disease early in neonatal life.

If Hirschsprung's disease requires diagnosis within the first several days of life to decrease the risk of enterocolitis, then a high index of suspicion and aggressive evaluation are necessary. The medical histories of the 51 neonates with Hirschsprung's disease in our series identify an abnormal stooling pattern characterized by delayed meconium passage, infrequent stools, or no spontaneous stools. As Swenson et al.[9] stated in 1973, ". . . it is clear that failure to pass meconium within the first 24 hours of life, . . . is the objective information which should alert the physician to the possibility of congenital megacolon." Implementation of Dr. Swenson's now classic observation would have most likely eliminated all but two of our neonatal and infant cases of HAEC.

The well-recognized association of trisomy 21 and Hirschsprung's disease has been reported in 3% of cases,[4,9] while more recent series note a 15% occurrence.[6,7] The higher incidence of trisomy 21 in our series (16%) allows for several observations. First, patients with trisomy 21 comprised one third of all cases of enterocolitis. Second, 46% of the infants and children with trisomy 21 developed HAEC in comparison to only 19% of patients without trisomy 21. Third, associated anomalies were present in three fourths of the patients with trisomy 21 but in only one fourth without trisomy 21. Fourth, the three deaths in our series occurred in patients with trisomy 21; one death was directly attributable to HAEC. The other two infants died of associated problems following recovery from an episode of enterocolitis. Based on these findings, we believe that Hirschsprung's disease in an infant or child with trisomy 21 should be viewed as a strong risk factor for development of enterocolitis. Patients with trisomy 21 have marked deficiencies in T cell-mediated cytotoxicity and in interferon production[10] and possible derangements in humoral immunity.[11] It may be that infants and children with trisomy 21 are more susceptible to HAEC and less immunologically capable of recovery. No study has addressed the functional integrity of gastrointestinal immunity in patients with trisomy 21 and Hirschsprung's disease.

Enterocyte-adherent organisms were present in the colonic specimens in one third of our patients with HAEC. These organisms were not identified in the tissue specimens of patients without enterocolitis. Enterocyte-adherent organisms may have a role in the pathogenesis of HAEC, or the presence of enterocolitis may predispose the intestinal mucosa to attachment of enterocyte-adherent organisms. *Clostridium difficile* toxin has been isolated more frequently from young children with HAEC than from healthy patients with Hirschsprung's disease,[12] suggestive of a possible causal relationship.

Previous authors have reported that infants and children with long-segment aganglionosis are at an increased risk to develop enterocolitis.[3,4] Patients in our study with longer levels of aganglionosis (transverse and total colon) did not acquire HAEC more frequently than patients with rectosigmoid disease. Most likely, this discrepancy relates to the majority of our cases of long-segment aganglionosis achieving diagnosis and treatment in the neonatal period.

An initial episode of enterocolitis at diagnosis of Hirschsprung's disease has been considered a predisposing factor for further episodes.[5,9] However, recurrent HAEC occurred in only two cases (15%) in our series, one of which developed after a pull-through procedure complicated by an anorectal stricture. In the second case an infant with trisomy 21 acquired a diffuse, fatal enterocolitis 6 weeks following recovery from his first episode of HAEC.

Enterocolitis acquired after a pull-through procedure was most frequently the result of an anorectal stricture in our series. Standard diagnostic investigation including barium enema, rectal biopsy, and anal manometry was helpful in elucidating the etiology of the dysfunctional pull-through procedure. Following appropriate secondary operations to relieve the anorectal stricture, no child suffered additional episodes of HAEC.

Neonatal enterocolitis at diagnosis of Hirschsprung's disease imposes the risk of increased morbidity and extended hospitalization. One third of the neonates with HAEC in our series experienced a major complication requiring a second operative procedure. The dilated, thin-walled, and friable colon with enterocolitis must be handled with meticulous, gentle technique, and the colostomy must be carefully constructed to avoid postoperative evisceration and stomal prolapse. Neonates with HAEC were hospitalized twice as long as neonates without enterocolitis, and they incurred significantly higher medical expenses.

The low mortality rate of 5% for patients with HAEC in our series compares favorably with other reports.[3,5] This low mortality rate is misleading, however, because two infants died from other causes (cardiac disease and aspiration) immediately after recovery from an enterocolitis episode.

We conclude that enterocolitis continues to be a major cause of morbidity and mortality in infants and children with Hirschsprung's disease. Elimination of neonatal enterocolitis requires diagnosis of Hirschsprung's disease within the first several days of life. Significant risk factors for HAEC include a delay in diagnosis beyond 1 week of age and the presence of trisomy 21. Although neonates with enterocolitis have a longer and costlier hospitalization, recovery without recurrent episodes of HAEC can be anticipated for most patients.

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*Dosage adjustment, based on estimated creatinine clearance, may be necessary in elderly patients.

For a discussion of INDICATIONS AND USAGE (including susceptible organisms), CONTRAINDICATIONS, PRECAUTIONS, and ADVERSE REACTIONS, please consult brief summary on adjacent page.

†Demonstrated in animal studies, and in human volunteer studies involving 36 subjects. In clinical trials involving 4,570 subjects, transient elevations in serum creatinine were rarely observed.

‡Renal function should be monitored when AZACTAM (aztreonam) is used concomitantly with aminoglycosides. In patients with impaired hepatic or renal function, appropriate monitoring is recommended during therapy.

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NDICATIONS AND USAGE—Before initiating treatment with AZACTAM, appropriate specimens should be obtained for isolation of the causaive organism(s) and for determination of susceptibility to aztreonam. Treatment with AZACTAM may be started empirically before results of he susceptibility testing are available; subsequently, appropriate anibiotic therapy should be continued.

AZACTAM For Injection is indicated for the treatment of the followng infections caused by susceptible gram-negative microorganisms: **Urinary Tract Infections** (complicated and uncomplicated), including pyelonephritis and cystitis (initial and recurrent) caused by *Escheichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Enterobacter cloacae, Klebsiella oxytoca**, *Citrobacter* species* and *Serratia marcescens**. **Lower Respiratory Tract Infections**, including pneumonia and bronchitis caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Haemophilus influenzae, Proteus mirabilis, Enterobacter* species and *Serratia marcescens**. **Septicemia** caused by *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis**, *Serratia marcescens** and *Enterobacter* species. **Skin and Skin-Structure Infections**, includng those associated with postoperative wounds, ulcers and burns caused by *Escherichia coli, Proteus mirabilis, Serratia marcescens, Enterobacter* species, *Pseudomonas aeruginosa, Klebsiella pneumoniae*, and *Citrobacter* species*. **Intra-abdominal Infections**, including peritonitis caused by *Escherichia coli, Klebsiella* species, including *K. pneumoniae, Enterobacter* species including *E. cloacae**, *Pseudomonas aeruginosa, Citrobacter* species* including *C. freundii** and *Serratia* species* including *S. marcescens**. **Gynecologic Infections**, ncluding endometritis and pelvic cellulitis caused by *Escherichia coli, Klebsiella pneumoniae**, *Enterobacter* species* including *E. cloacae**, and *Proteus mirabilis**.

AZACTAM is indicated for adjunctive therapy to surgery in the management of infections caused by susceptible organisms, including abscesses, infections complicating hollow viscus perforations, cutaneous infections and infections of serous surfaces. AZACTAM is efective against most of the commonly encountered gram-negative aerobic pathogens seen in general surgery.

Concurrent Therapy—Concurrent initial therapy with other antimicrobial agents and AZACTAM is recommended before the causative organism(s) is known in seriously ill patients who are also at risk of having an infection due to gram-positive aerobic pathogens. If anaerobic organisms are also suspected, therapy should be initiated using an antianaerobic agent concurrently with AZACTAM. Certain antibiotics (e.g., cefoxitin, imipenem) may induce high levels of beta-lactamase *in vitro* in some gram-negative aerobes such as *Enterobacter* and *Pseudomonas* species, resulting in antagonism to many beta-lactam antibiotics including aztreonam. These *in vitro* findings suggest that such beta-lactamase inducing antibiotics not be used concurrently with aztreonam. Following identification and susceptibility testing, appropriate antibiotic therapy should be continued.

CONTRAINDICATIONS—Aztreonam is contraindicated in patients with known allergy to this antibiotic.

WARNINGS—Careful inquiry should be made for a history of hypersensitivity reaction to any antibiotic or other drugs. Antibiotics should be given with caution to any patient who has had some form of allergy, particularly to drugs. It is recommended that patients who have had immediate hypersensitivity reactions (e.g., anaphylactic or urticarial) to penicillins and/or cephalosporins should be followed with special care. If an allergic reaction to aztreonam occurs, discontinue the drug and institute supportive treatment as appropriate (e.g., maintenance of ventilation, pressor amines, antihistamines, corticosteroids). Serious hypersensitivity reactions may require epinephrine and other emergency measures.

PRECAUTIONS—General: In patients with impaired hepatic or renal function, appropriate monitoring is recommended during therapy. If an aminoglycoside is used concurrently with aztreonam, especially if high dosages of the former are used or if therapy is prolonged, renal function should be monitored because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. The use of antibiotics may promote the overgrowth of nonsusceptible organisms, including gram-positive organisms and fungi. Should superinfection occur during therapy, appropriate measures should be taken.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Carcinogenicity studies in animals have not been performed. Genetic toxicology studies performed *in vivo* and *in vitro* with aztreonam in several standard laboratory models revealed no evidence of mutagenic potential at the chromosomal or gene level. Two-generation reproduction studies in rats at daily doses up to 20 times the maximum recommended human dose, prior to and during gestation and lactation, revealed no evidence of impaired fertility. There was a slightly reduced survival rate during the lactation period in the offspring of rats that received the highest dosage, but not in offspring of rats that received five times the maximum recommended human dose.

Pregnancy—Pregnancy Category B: Aztreonam crosses the placenta and enters the fetal circulation. Studies in pregnant rats and rabbits, with daily doses up to 15 and 5 times, respectively, the maximum recommended human dose, revealed no evidence of embryo- or fetotoxicity or teratogenicity. No drug induced changes were seen in any of the maternal, fetal or neonatal parameters that were monitored in rats receiving 15 times the maximum recommended human dose of aztreonam during late gestation and lactation. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, aztreonam should be used during pregnancy only if clearly needed.

Nursing Mothers—Aztreonam is excreted in breast milk in concentrations that are less than 1% of concentrations determined in simultaneously obtained maternal serum; consideration should be given to temporary discontinuation of nursing and use of formula feedings.

Pediatric Use—Safety and effectiveness have not been established in infants and children.

ADVERSE REACTIONS—Local reactions such as phlebitis/thrombophlebitis following IV administration, and discomfort/swelling at the injection site following IM administration occurred at rates of approximately 1.9% and 2.4%, respectively. Systemic reactions (considered to be related to therapy or of uncertain etiology) occurring at an incidence of 1 to 1.3% include diarrhea, nausea and/or vomiting, and rash. Reactions occurring at an incidence of less than 1% are listed within each body system in order of decreasing severity: *Hypersensitivity*—anaphylaxis. *Hematologic*—pancytopenia, neutropenia, thrombocytopenia, anemia, leukocytosis, thrombocytosis. *Gastrointestinal*—abdominal cramps; rare cases of *C. difficile*-associated diarrhea or gastrointestinal bleeding have been reported. *Dermatologic*—purpura, erythema multiforme, urticaria, exfoliative dermatitis, petechiae, pruritus, diaphoresis. *Cardiovascular*—hypotension, transient ECG changes (ventricular bigeminy and PVC). *Respiratory*—one patient experienced flushing, chest pain, and dyspnea. *Hepatobiliary*—hepatitis, jaundice. *Nervous System*—seizure, confusion, vertigo, paresthesia, insomnia, dizziness. *Musculoskeletal*—muscular aches. *Special Senses*—tinnitus, diplopia, mouth ulcer, altered taste, numb tongue, sneezing and nasal congestion, halitosis. *Other*—vaginal candidiasis, vaginitis, breast tenderness. *Body as a Whole*—weakness, headache, fever, malaise.

Adverse Laboratory Changes—Those reported without regard to drug relationship during clinical trials were: *Hepatic*—elevations of AST (SGOT), ALT (SGPT), and alkaline phosphatase; signs or symptoms of hepatobiliary dysfunction occurred in less than 1% of recipients (see above). *Hemic*—increases in prothrombin and partial thromboplastin times, eosinophilia, positive Coombs test. *Renal*—increases in serum creatinine.

OVERDOSAGE—If necessary, aztreonam may be cleared from the serum by hemodialysis and/or peritoneal dialysis.

DOSAGE AND ADMINISTRATION—Dosage adjustments are recommended for patients with impaired renal function. In elderly patients, estimates of creatinine clearance should be obtained and appropriate dosage modifications made if necessary.

HOW SUPPLIED—AZACTAM For Injection (Aztreonam For Injection) is supplied in single-dose 15 mL vials containing **500 mg, 1 g** or **2 g** per vial, and in single-dose 100 mL intravenous infusion bottles containing **500 mg, 1 g** or **2 g** per bottle.

Consult package insert before prescribing AZACTAM (aztreonam).

(J4-140)

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*Efficacy for this organism in this organ system was studied in fewer than ten infections.

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A New Mechanical Device for Circular Compression Anastomosis

Preliminary Results of Animal and Clinical Experimentation

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The authors report the preliminary results obtained in animal and clinical experimentation of a new mechanical device for circular anastomosis which they have developed. It is a gun that places an apparatus consisting of three polypropylene rings that, through the compression among them of the severed edges of the bowel, realize a sutureless anastomosis and are spontaneously evacuated. Fifty-eight colonic anastomoses were performed in dogs with this device; 23 stapled colonic anastomoses were also executed concurrently. Forty-four animals underwent a relaparotomy to remove the colonic specimen containing the anastomoses. Bursting pressure and the histologic features of the anastomoses were evaluated at different time intervals after operation. A good healing of all compression anastomoses was observed, thereby allowing them to initiate the experience in humans. Thirteen anastomoses (6 colorectal extraperitoneal, 1 colorectal intraperitoneal, 5 colocolonic, 1 ileorectal) were performed at the 1st Surgical Department, Milan University. One subclinical leakage (7.7%) spontaneously healed in a few days. No stenoses were observed.

THE USE OF compression anastomotic devices in the intestine as a temporary support to the tissue to allow for a natural healing process, has been known since the last century. Denans,[1] in 1826, invented the first compression device, thus starting a new technology that would form the basis for all future mechanical devices for anastomosis. Dr. Murphy,[2] in his original article in 1892, outlined the following: "What are the best means and methods of producing agglutination of surfaces and preventing subsequent contraction at the point of adhesion? If means can be divised—1, to hold surfaces in contact; 2, while in contact to provide a speedy and permanent adhesion of the surfaces; 3, to keep an opening sufficiently large for the free passage of intestinal content; 4, to produce, as a result, a cicatrix that will not contract to any greater extent, and by the contraction produce complete or partial obstruction—we will overcome the great barriers that still remain between us and ideal success in intestinal surgery." Murphy's "anastomotic button" was then introduced as the solution of the problems encountered in hand-sewn anastomoses. This procedure proved to be safe because the force produced by the button was distributed around the entire circumference of the anastomosis producing a watertight seal. The natural healing of this anastomosis caused the whole button to be eliminated. Thus no foreign bodies, which all induce stenosis, were left at the anastomotic site.

Nevertheless, the Murphy button and other compression devices[2-4] received limited acceptance throughout the surgical community. This was partially due to the fact they were difficult to use because they were placed manually with considerable bowel manipulation.

Recently, a device that performs compression anastomosis has been developed in the Soviet Union showing good clinical results.[5] With such a resurgence of interest on this matter, we developed and experimented a new mechanical device that realizes compression anastomoses placing endoluminally an apparatus consisting of three polypropylene rings. This paper presents the preliminary results we have obtained in animal experimentation in dogs and the initial human application of this device.

Methods

Materials

The anastomotic apparatus object of this paper consists of three molded polypropylene rings. These are an outer, an intermediate, and an inner ring (Fig. 1). They are carried by a gun that introduces them into the bowel, realizes their assemblage and their automatic disengage-

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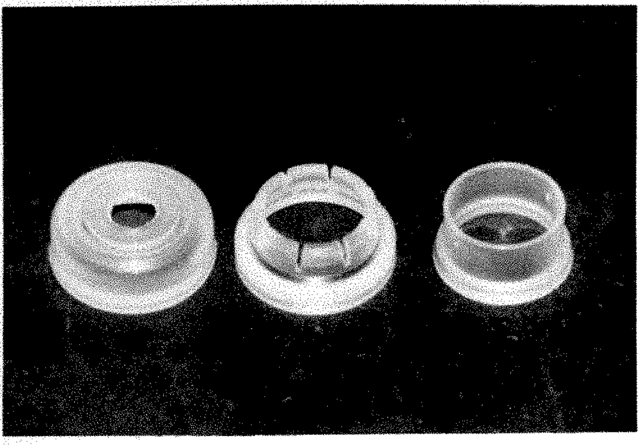


FIG. 1. The three rings of the anastomotic apparatus shown are from left to right: the outer, the intermediate, and the inner.

ment, being subsequently removed. The outer ring has the shape of an overturned bowl: it is stiff and it can hold, into its concavity , the conic-shaped intermediate ring that has an upper portion with multiple longitudinal slots. The inner cylindrical ring is also stiff. Once the intermediate ring is inserted into the outer ring, which is an easy maneuvre for the conic shape of the former, the assemblage of the system is realized when the inner ring is forced and fits into the intermediate ring. Thus, the upper portion of the latter, which is extensible for the longitudinal slots, expands while clinging into the concavity of the outer ring. The system, which realizes the compression of the bowel ends between the internal surface of the outer ring and the external surface of the intermediate ring, forms a firm, perfectly tight block. Two different sizes of rings are currently available: 30 mm and 25 mm outer diameter.

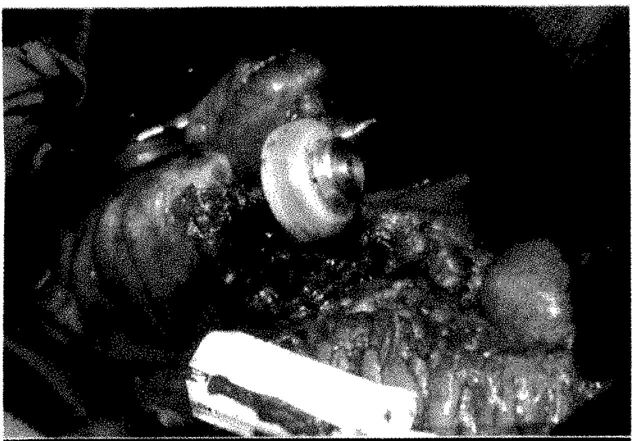
The gun carrying the anastomotic apparatus is composed of a head portion consisting of the ring holders and of a circular blade, a middle part consisting of coaxial tubular members that transmit the movements needed to realize the assemblage and the expulsion of the rings, and a body consisting of the handle and of the mechanisms regulating these movements.

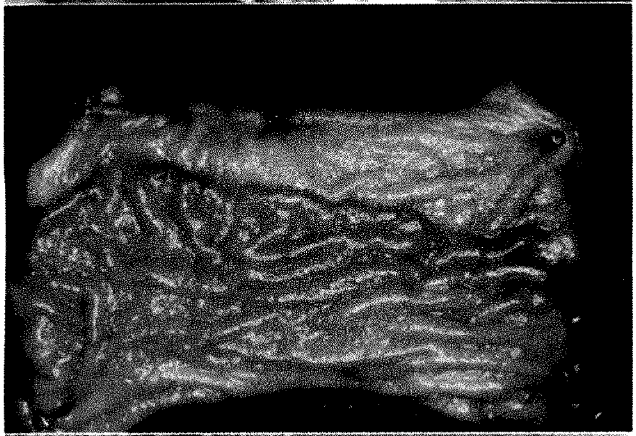
The intermediate ring is secured on the head that contains, just behind it, the inner ring. The outer ring is installed on the central shaft as the staplers anvil. To allow the assemblage and the expulsion of the rings, the outer ring is brought to a settled distance of 1.2 mm from the intermediate ring. By operating the lever of the gun, a series of movements is produced that causes the assemblage of the rings that cling together, and their automatic expulsion by means of a circular blade that, together with the tissue edges tied by the purse-string sutures, cuts also the outer ring at its joint to the central shaft. The extraction of the gun does not require any additional maneuvre, thus avoiding dangerous tractions on the anastomosis. The inner diameter of the anastomotic apparatus then results in 17.5 mm for the bigger rings and 12.5 mm for the smaller rings.

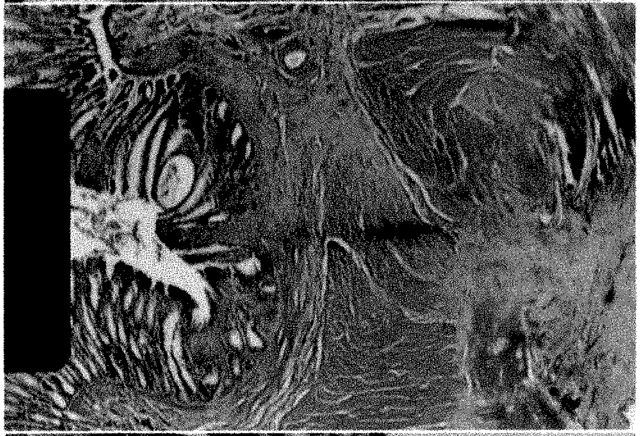
The surgical technique needed for the use of this gun, that allows the realization of end-to-end and end-to-side anastomoses, is similar to what is currently done when using staplers.[6] A colorectal anastomosis is an example of this technique. After removal of the rectum and sigmoid, the proximal colon is prepared by removing paracolonic fat and devascularizing it 1.5 cm from the severed edge where a purse-string suture has been previously placed. The gun is then lubricated with sterile lubricating oil and introduced transanally. The gun is slid into the bowel until the outer ring has exited from the rectal stump. Its central shaft, carrying the outer ring, is then extended and the distal purse-string suture is tied drawing the tissue around the intermediate ring (Fig. 2). The outer ring is then inserted into the colonic stump and the proximal purse-string suture is tied around the central shaft drawing the tissue over the outer ring. The central shaft is driven backward approximating the outer ring to the settled distance of 1.2 mm from the intermediate ring. During the approximation of the two anastomotic ends, care must be taken to avoid kinking of the bowel and to have a good serosa-to-serosa interface. Next, the gun is fired by operating the handle. This causes simultaneous assemblage of the rings, expulsion of the entire anastomotic apparatus, and disengagement of the gun from the anastomosis. The two tissue "doughnuts" cut by the circular blade must be, as for staplers, carefully inspected for completeness to ensure that the tissue ends are comprised between the rings. The anastomosis is achieved in this manner leaving only the three plastic rings at the anastomotic site. A drain, if necessary, should not be placed directly in contact with the anastomosis. This avoids possible decubitus lesions of the colonic wall that could be compressed between two stiff bodies: the rings inside the lumen and the drain tube outside. The rings will fall into the bowel lumen and will be evacuated. Their detachment takes place when a natural healing of the anastomosis is achieved outside the compressed area.

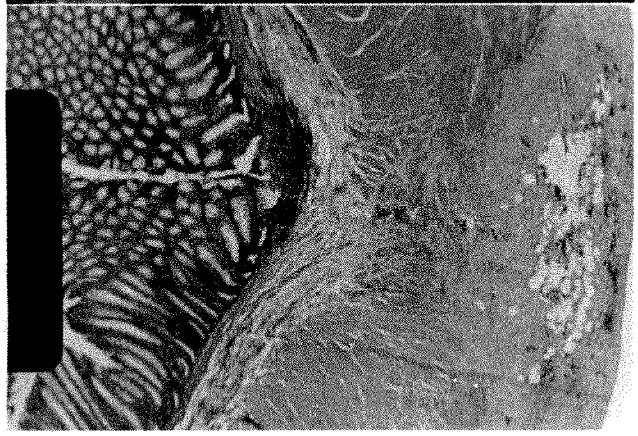
Animal Experimentation

This device was used in dogs to perform 58 colonic anastomoses, 23 times using rings of 30 mm and 35 times using the 25-mm rings. Twenty-three stapled anastomoses were performed twice using the 28 and 11 times using the 25 disposable EEA® (Autosuture, United States Surgical Corporation, Norwalk, CT); six times using the 29 and four times using the 25 ILS® (Ethicon, Sommerville, NJ). In 21 animals the new device and circular stapler were used concurrently. Condi-









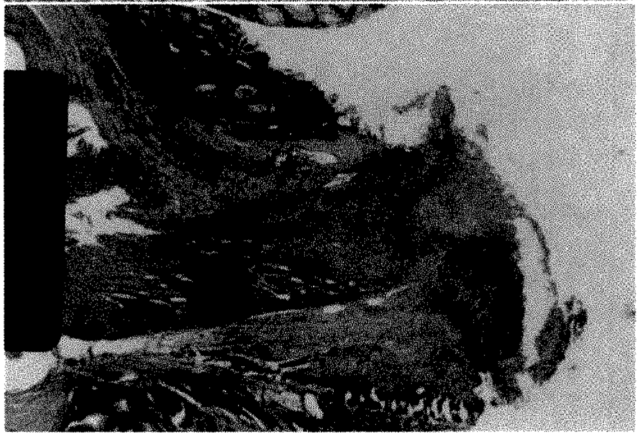


FIG. 2. (*top left*). Operative picture: the gun has been inserted transanally and the distal purse-string suture has been tied around the central shaft. The outer ring will be inserted into the proximal stump. **FIG. 3.** (*top right*). How the compression anastomosis appears after 85 days from its realization. No adhesions are evident at the site of the anastomosis. **FIG. 4.** (*middle left*). How the compression anastomosis appears at longitudinal opening of the intestinal lumen. No signs of hypertrophic scarring are present. **FIG. 5.** (*middle right*). Section of a compression anastomosis 6 days after its realization: a satisfactory alignment of the tissue layers and an initial mucosal re-epithelization are present. **FIG. 6.** (*bottom left*). Complete healing of a compression anastomosis 85 days after its realization: the process of mucosal re-epithelization is completed. **FIG. 7.** (*bottom right*). Section of a stapled anastomosis 6 days after its realization: the two mucosal surfaces are separated by an overgrowing scar tissue.

tioned dogs ranging in size from 7 to 23 kg (average 14.5 kg) were used for this study following institutional guidelines for the care and use of laboratory animals. They had a preoperative preparation of a liquid diet for 24 hours and an enema the evening before and the morning of surgery. They were operated on under general anesthesia using intravenous pentobarbital and Ethrane gas. The dogs received antibiotic prophylaxis in the form of penicillin administered intramuscularly and sterile operative technique was followed. The gun was inserted into the bowel twice through a distal colotomy and 56 times through the anus, whereas circular staplers were always introduced transanally. The bowel was prepared by devascularizing and removing all pericolonic

TABLE 1. *Surgical Controls**

Postoperative Day	Compression Anastomoses	Stapled Anastomoses
2	3	3
3	6	2
4	3	1
5	6	4
6	2	2
7	4	2
8	1	1
9	4	2
11	1	0
14	1	1
15	5	0
21	2	1
30	2	0
65	1	0
82	1	0
85	2	0
Total	44	19

* Number of compression and stapled anastomoses that underwent surgical controls through relaparotomy at different postoperative time intervals.

fat within approximately 1.5 cm of the anastomotic ends. After each anastomosis, the devices were checked to assure that complete tissue doughnuts were dissected by the circular blades. In the colon containing both stapled and compression anastomoses, the former was always located in the proximal colon, whereas the latter was located in the distal colon or in the intraperitoneal rectum. No drainage tubes were placed nor was omentoplasty performed. After operation the dogs were given hypodermic 5% glucose 250 ml and water for 2 days after which a normal laboratory diet was resumed.

The anastomoses were evaluated as follows: (1) clinical controls—the dogs were examined daily. First bowel movements and expulsion of the rings were recorded. (2) Surgical controls—44 animals underwent relaparotomy, and the intestinal segment containing the anastomoses was resected at different postoperative days (Table 1). (3) Bursting pressure—the bursting pressure was tested on 23 compression and 14 stapled anastomoses, and on 13 sections of intact colon at different postoperative days (Table 2). The sections were: just distal to the cecum for the intact colon, midcolonic for the stapled anastomoses, and distal colonic or proximal rectal for the compression anastomoses. After the excised segments of colon were emptied of feces, one of the two ends was tied to a plastic nipple. The segment was flushed with water and collapsed while the other end was tied off. The nipple was connected to a syringe and to a pressure transducer attached to a strip chart recorder. Pressure values for tears or burst were recorded. (4) Histologic evaluation—macro- and microscopic evaluation were carried out on 19 compression and 7 stapled anastomoses at different postoperative intervals (Table 3). Hematoxylin and eosin staining was utilized. The alignment of the layers at the anastomotic site was specifically evaluated. In examination of the stapled anastomoses, the staples, when present, were gently removed to allow the specimen to be taken into thin sections.

TABLE 2. *Bursting Pressure (mmHg)**

Postoperative Day	Compression Anastomoses	Stapled Anastomoses	Intact Colon
0	240, 350, 495	100,‡ 123,‡ 150‡	
2	72,‡ 156‡	108,‡ 114‡	198, 246
3	66,† 68,† 90,‡ 96,‡ 125‡	118,‡ 192‡	276, 312 318, 318
5	100,‡ 125,‡ 138‡ 170,‡ 180,‡ 210‡	152,‡ 246‡	264, 444, 477
7	280, 318,‡ 402	348, 348	410, 504
9	360, 402, 500	330, 384	378, 396
11	200		

* Bursting pressure values in compression and stapled anastomoses and in specimens of intact colon at different postoperative time intervals.

† Specimen damaged at removal.

‡ Anastomotic tear.

TABLE 3. *Histologic Controls**

Postoperative Day	Compression Anastomoses	Stapled Anastomoses
2	1	1
4	1	1
6	2	2
7	1	0
8	1	1
14	1	1
15	5	0
21	2	1
30	2	0
65	1	0
85	2	0
Total	19	7

* Number of compression and stapled anastomoses that underwent histologic controls at different postoperative time intervals.

Human Experimentation

Thirteen patients underwent large bowel compression anastomosis at the 1st Department of Surgery, Milan University, Milan, Italy. They were 10 males (age: 41–73 years, mean: 60.6 years) and three females (age: 48–60 years, mean: 52.6 years). Eight adenocarcinomas, two villous adenomas with severe dysplasia, one sigmoid diverticulitis, one megacolon with severe constipation, and one rectovaginal fistula after hysterectomy were the indications for surgery. All patients underwent mechanical colonic preparation and parenteral antibiotic prophylaxis with a cephalosporine. The gun was always introduced transanally according to the technique previously described. The larger ring sizes (30 mm OD) were used 11 times and the smaller rings (25 mm OD) were used twice. Seven anterior resections of the rectum-sigmoid (six times with extraperitoneal colorectal anastomosis), five left colonic resection with colocolonic anastomosis, and one total colectomy with intraperitoneal ileorectal anastomosis were performed. The tissue doughnuts cut by the circular blade were always inspected, and pneumatic control (air inflation of the anastomosis plunged under water) of the anastomosis was always carried out. A drain tube was always placed near the anastomosis. Two diverting colostomies were performed on the first very low anastomosis (the second patient of the series) and on the resection of the rectum for rectovaginal fistula, respectively. The first colostomy was closed 3 months after the operation, whereas the second one was removed on the 20th postoperative day. In one case the resection was enlarged to the dome of the urinary bladder and in another case to the uterus and ovaries. Nasogastric suction was maintained until bowel movements resumed, which then allowed oral feeding. The stools of the patients were always carefully inspected to find the anastomotic rings. Patients were discharged from the hospital only after the evacuation of the rings. All patients were controlled endoscopically 1, 3, 6, and 12 months after surgery; contrast enema were performed once a year according to our follow-up protocol for colorectal cancer (F.O.N.C.A.D.: Forza Operativa Nazionale per il Carcinoma dell'Apparato Digerente).

Results

Animal Experimentation

Clinical. One dog, who underwent both a compression and a stapled anastomosis, was not included in the study because of a technical error in the surgical procedure. At the time of operative inspection, the tissue ring cut by the circular blade of the compression anastomosis device was found to be incomplete. We decided not to redo the anastomosis and therefore had the only failure of the entire series. The postoperative course was normal for the other dogs. Normal bowel movements returned between the 2nd and 3rd postoperative day. The anastomotic rings were expelled between the 3rd and 6th postoperative day in all but one dog in which they were found in the stool at the 12th postoperative day.

Surgical. No leakages were found in the 44 compression and the 19 stapled anastomoses. In one case, a small paranastomotic abscess was found near the handsewn closure of the colotomy performed for the introduction of the device into the bowel. Compression anastomoses were found, in the majority of the cases, without or at most with very weak anastomotic adhesions (Fig. 3). In only two cases were significant adhesions found covering more than 270° of the anastomosis. In 12 of the 19 stapled anastomoses, no adhesions or at most very weak ones were found; they were covering more than 270° of the anastomosis in the remaining seven. In the 13 compression anastomoses controlled after more than 15 days from surgery (15–85 days, mean: 38 days), no signs of stenosis were detected.

Bursting pressure. Of the 24 compression anastomoses, one could not be evaluated because it broke at the time of removal and two were partially damaged but could be tested; they all were 3 day specimens. One of the 14 stapled anastomoses could not be evaluated because it also broke but at removal five days after operation. The results are shown in Table 2. As for compression anastomoses, colonic rupture occurred out of the anastomotic line at a pressure between 240 and 495 mmHg when the test was carried out immediately after the placement of the rings (time 0). It occurred at the anastomosis for the specimen tested on the 2nd, 3rd, and 5th day at a pressure between 72 and 210 mmHg, and at a pressure of 318 mmHg in one specimen on the 7th day. An extra-anastomotic rupture was recorded at a pressure between 200 and 500 mmHg in the two other 7 day specimens and in the 9 and 11 day specimens. In the two 3 day specimens partially damaged at removal, the anastomotic rupture occurred at a pressure of 66 and 68 mmHg, respectively. As for stapled anastomoses, colonic rupture occurred at the anastomosis for specimen at time 0 and on the 2nd, 3rd, and 5th day at a pressure between 100 and 246 mmHg; it was extra-anastomotic at a pressure between 330 and 384 mmHg for the 7 and 9 day specimens. In the removed proximal "normal" colon, a decrease in the bursting pressure values in the early postoperative time followed by an increase on the 5th day was observed.

Histologic features. Macroscopic appearance of compression anastomoses at the longitudinal opening of the bowel was always good. No signs of hypertrophic scar tissue were detected (Fig. 4). The stapled anastomoses were also good even though a circular fibrotic ring was almost always present. Microscopically, all the intestinal layers showed a good alignment on compression anastomoses. A rapid re-epithelization of the mucosa was observed. No signs of inflammation or at most only moderate signs were detected (Figs. 5 and 6). Stapled anastomoses showed a moderately good alignment of intestinal wall layers. At the anastomosis, a wide area of granulation tissue with lack of re-epithelization was constantly present. A prolonged chronic inflammation due to foreign bodies was also always observed (Fig. 7).

Human Experimentation

Canalization to gases resumed as usual between the 3rd and 5th postoperative day. Canalization to feces oc-

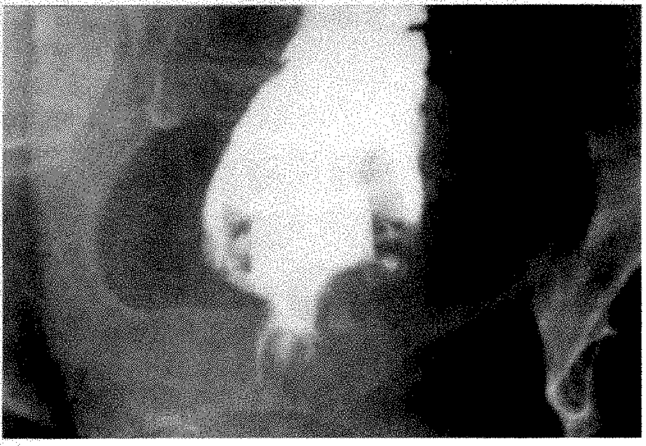


FIG. 8. Enema with liquid contrast of a low colorectal anastomosis at the 7th postoperative day. The rings are still in place and the contrast easily passes through the anastomotic apparatus.

curred between the 5th and 9th postoperative day, not affected by the presence of the rings at the anastomotic site (see Fig. 8). The rings were evacuated between the 8th and 13th postoperative day (mean: 11.2) without causing any discomfort to the patients. No significant postoperative fever was recorded. As for postoperative complications, we observed one (7.7%) subclinical leakage: it appeared in a very low colorectal anastomosis on the 7th postoperative day, revealed by the presence of fecal material in the drainage tube. No fever, peritonitis, or other general symptoms were registered. The rings were still present at the anastomotic site and the patient had regular evacuations. An enema performed on the 9th postoperative day showed the immediate drainage of the liquid contrast medium through the tube that was in contact with the colonic wall at the anastomotic site. The patient healed in 8 days by just progressively withdrawing the tube without needing a diverting colostomy. No other complications were observed. At radiologic and endoscopic long-term controls, wide anastomoses were observed without evidence of strictures (Fig. 9). The anastomotic line was often difficult to recognize even *via* videoendoscopic controls.

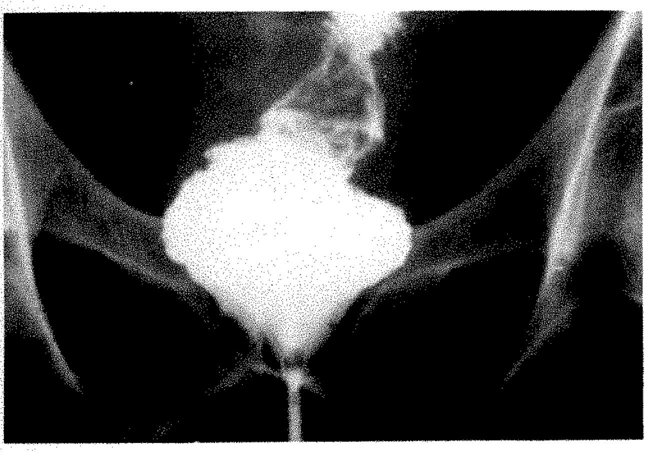


FIG. 9. Enema with liquid contrast of a low colorectal anastomosis at the 13th postoperative day. The rings have been evacuated and the anastomosis is wide.

Discussion

Anastomotic buttons, realizing a sutureless anastomosis through the compression of the edges of the intestinal stumps, have elicited a great debate in gastrointestinal surgery over the last 150 years.[1-4] In fact, even if the concept was well accepted by the majority of surgeons, the mechanical means for its realization have been considered inappropriate. Murphy's and other anastomotic buttons were mainly criticized for their narrow inner caliber and their difficult placement and assemblage that required a contaminating surgical technique. Furthermore there were no satisfactory control means for their correct positioning.

The Soviets have recently introduced a device, AKA-2, which places compression anastomotic rings. This gun has been used with good clinical results in colorectal surgery.[5,7] The rings, made of a plastic material, are held together by a series of metal pins provided with small coaxial springs. The gun is reusable and needs to be assembled and loaded at the time of surgery.

The device we developed places molded polypropylene rings, which are assembled by clinging one into each other. In the current study we used a steel reusable prototype: a completely disposable device is currently under study. The surgical technique to be followed for the execution of the anastomosis is similar to that usually used for staplers.[6] However, extraction of the gun from the anastomosis, which is a challenging maneuvre with staplers,[8,9] is automatic with this device. In fact, after cutting the bowel edges closed by the two purse-string sutures around the central shaft, the circular blade also cuts the central part of the outer ring. This, together with the thrust of the intermediate ring out of its site by means of the inner ring, realizes the automatic disengagement from the gun of the three joined rings. Therefore, the execution of the anastomosis is concurrent with the extraction of the gun.

The tissue doughnuts cut by the circular blade must be, as for staplers, carefully inspected.[10] They must be complete to ensure that the tissue ends are comprised between the rings. We observed in a dog the outcome of a technically incorrect anastomosis (the one with incomplete doughnuts that was, therefore, not included in the evaluation) and we registered the only leakage of our experimental series. Thus, we believe that this control is of the utmost importance for a successful outcome of the anastomosis.

The canalization with regular stool evacuation was not impaired by the presence of the rings. Even with smaller size rings (25 mm O.D.) at the anastomotic site, a normal evacuation of solid stool was recorded.

At reoperative controls, compression anastomoses always appeared good and just a thin pale line was often visible from outside. In the specimen containing both the anastomoses, the compression ones were always at a lower site than stapled ones, sometimes even being colorectal. No leakages, which also in animals are more frequently reported for anastomoses involving the rectum,[11] were recorded in these experimental series. Anastomotic adhesions account for a lower percentage of cases in compression than in stapled anastomoses. This is probably due to the fact that in the latter, foreign bodies, like staples, are prominent also from the serosal side.

Due to the small figures, no statistical evaluation was performed on the bursting pressure values. With the rings at the anastomotic site, tears of the intestinal wall were extra-anastomotic immediately after their placement. They were anastomotic 2 days after surgery for pressure over 70 mmHg, a value normally referred to as satisfactory.[12] On the 3rd postoperative day, in all the examined specimens, the rings could still be found inside the intestinal lumen but were already detached from the anastomosis. The bursting pressure values were still over 90 mmHg in the undamaged anastomoses. Extra-anastomotic tears 1 week after surgery at high pressure values were again recorded. Considering that pressure values in a dog's colon range between 0 and 30 mmHg, the results we achieved in our experimentation seem encouraging.

Bursting pressure was also examined on intact colon specimens. The decreasing values we found in the early postoperative stages, with subsequent rise and stabilization, have multiple interpretations. Similar results were obtained by others in rat colons.[13-16] These were explained through an early postoperative increase of the collagenase activity concurrent with a reduction in the collagen content of the colonic wall.

Histologic examination has given the most significant data. In all the compression anastomoses, the alignment of the tissue layers was satisfactory and the mucosa showed a rapid re-epithelization without formation of a circular fibrotic ring. No signs or at most only moderate signs of inflammation were present. In the stapled anastomoses we examined, as observed by others,[17] the alignment of the intestinal wall layers was moderately good. At the site of the anastomosis, a wide area of granulation tissue with marked disepithelization was constantly present and a prolonged chronic inflammation due to foreign bodies was also observed. These data indicate that compression anastomoses heal more quickly than stapled ones.

With these encouraging results in animal experimentation, we decided to begin human investigation in colorectal surgery. The patients were previously informed they would be operated on with a new device under investigation and they gave us their permission. We started with low-risk patients in order not to affect the evaluation of possible complications. After ten cases with positive results, we admitted to the study patients with increased risk of complications. In fact, the device was successfully used on a 73-year-old man with cancer infiltrating the urinary bladder (anterior resection of the rectum with bladder resection) and on a 61-year-old woman with long-standing diabetes and a cancer infiltrating the uterus and left ovary (anterior resection of the rectum with hystero-ovaryotomy).

There were two diverting colostomies. The first was performed on the second patient in our series who had a colorectal anastomosis located 5 cm above the anal verge. He had no complications and no colostomies were performed later on patients operated on for low rectal cancer. The second colostomy was done recently on a patient operated on elsewhere for a hysterectomy and who complained of a rectovaginal fistula. At time of operation, due to the highly contaminating procedure of resecting the rectum, the fistula, and the vaginal fornix, we decided to protect the anastomosis with fecal diversion. After the evacuation of the rings on the 13th postoperative day, we studied the anastomosis with a liquid contrast enema and, as it appeared satisfactory, we were able to close the colostomy on the 20th day.

The only postoperative complication observed was a subclinical leakage. It appeared on the 7th day and the hypothesis that it was caused by a decubitus of the drainage tube on the colonic wall at the anastomotic site is strongly suggestive. Furthermore, it was of little importance and the patient healed by only withdrawing the tube without needing reoperation.

Long-term controls have all confirmed the good quality of the anastomoses that, radiologically and even endoscopically, were often difficult to identify.

Conclusion

The preliminary results were have obtained in this study indicate the object of this study to be a reliable anastomotic device. Biologically, there is no doubt that a sutureless anastomosis is the ideal concept, as believed by Murphy, and to which every surgeon must aim. Mechanically, the anastomotic apparatus proved reliable and the gun, when available as completely disposable, will satisfy the need for properly functioning device.

Further experimentation can be justified to achieve statistical significance in the results. Our application in humans showed encouraging preliminary results. A wider clinical experimentation is needed to confirm what we obtained; a multicentric trial would be advisable for this purpose.

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Pancreaticogastrostomy Following Pancreatoduodenectomy

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Operative death following pancreatoduodenectomy results essentially from a pancreatojejunal anastomosis leakage. Pancreaticogastrostomy has been used infrequently. Seventeen patients (12 with malignant tumors and 5 with chronic pancreatitis) have undergone pancreaticogastrostomy following pancreatoduodenectomy. There was no operative mortality rate and no pancreaticogastrostomy leakage. Our data agree with data concerning pancreaticogastrostomy published in literature; cumulative mortality rate including our results is 4.5% (6 out of 134 patients) with only one transient benign pancreatic fistula reported. Many advantages offered by this method can explain these positive results including trypsine neutralization by gastric acidity and the possibility of nasogastric aspiration on contact with the anastomosis. Furthermore, permeability of the pancreatic duct can be easily verified by endoscopic examination. However, external pancreatic insufficiency does not seem to occur in long-term follow-up. These results suggest that this simple and safe method merits a more widespread application.

THE MORTALITY RATE following pancreatoduodenectomy in most centers is approximately 7–20%.[1-5] In approximately 50% of the cases, the mortality rate seems to be related to a pancreaticojejunal anastomosis leakage.[6,7] Although a wide variety of methods of reconstruction after Whipple resection have been described, a method for preventing this leakage is still awaiting widespread recognition. Waught and Clagett[8] in 1944 performed the first human pancreaticogastrostomy. Despite the low mortality and morbidity rates encountered after pancreaticogastrostomy, this method has been used only occasionally.[9-17] Our early clinical results in 17 patients who have undergone a pancreaticogastrostomy are reported here.

Methods

Technical Aspects

After removal of the head of the pancreas with the entire duodenum and the distal part of the stomach, the transected surface of the remaining pancreas, proven free of tumor, was freed from retroperitoneal attachment for 1–2 cm.

A corresponding transverse opening of about 3 cm was made on the posterior gastric wall, and the anastomosis was performed with an interrupted row of 3/0 polyglycolic acid sutures. Each stitch was passed through the pancreas, through the main duct, especially when the duct was dilated, and through the seromuscular layer of the stomach (Fig. 1). The posterior row of sutures was tied from the inside and the anterior row from the outside. Biliary anastomosis was then performed, followed by gastrojejunal anastomosis approximatively 30/40 cm distal to it (Fig. 2). Cholecystectomy was performed in all patients but not vagotomy. Drainage was placed to the right and posterior of the pancreaticogastrostomy. Nasogastric aspiration was left in place until the return of intestinal activity.

Patients

From September 1981 to December 1986, 17 patients (average age: 60 years, ranging from 34–81 years) underwent pancreatoduodenectomy with pancreaticogastrostomy. Twelve patients had malignant tumors (7 pancreatic adenocarcinoma, 3 duodenum cancer, 1 ampullary cancer, and 1 sarcoma). Five patients had chronic pancreatitis on histologic examination.

No reprints available.

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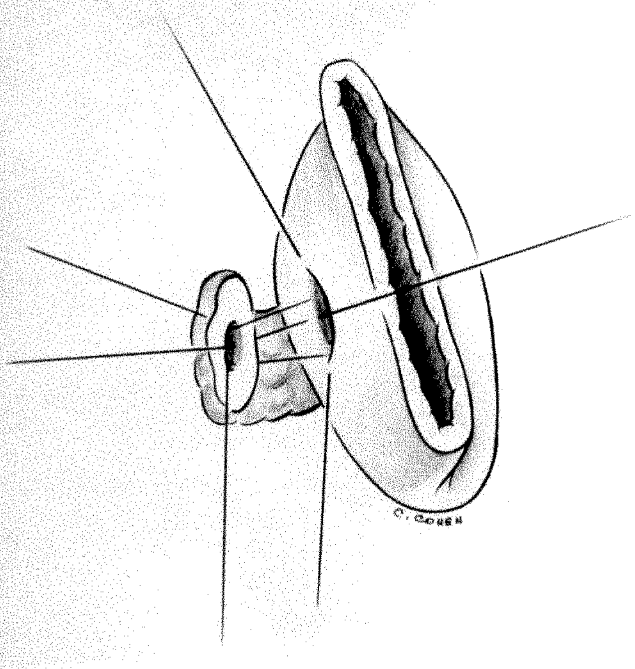

FIG. 1. Row of interrupted 3/0 sutures between the anterior surface of the pancreas and the posterior wall of the stomach.

Results

The major results were as follows: (1) there was no operative mortality rate; (2) no pancreatogastric anastomosis leakage occurred; and (3), postoperative complications occurred in two patients. One patient had peritoneal bleeding due to a breakdown of hemostasis on a collateral of the mesenteric superior vein, which was controlled by prompt reoperation. Another patient had continuous gastrointestinal bleeding. Endoscopic examination and reoperation with gastrostomy failed to reveal the origin of this bleeding, which stopped spontaneously.

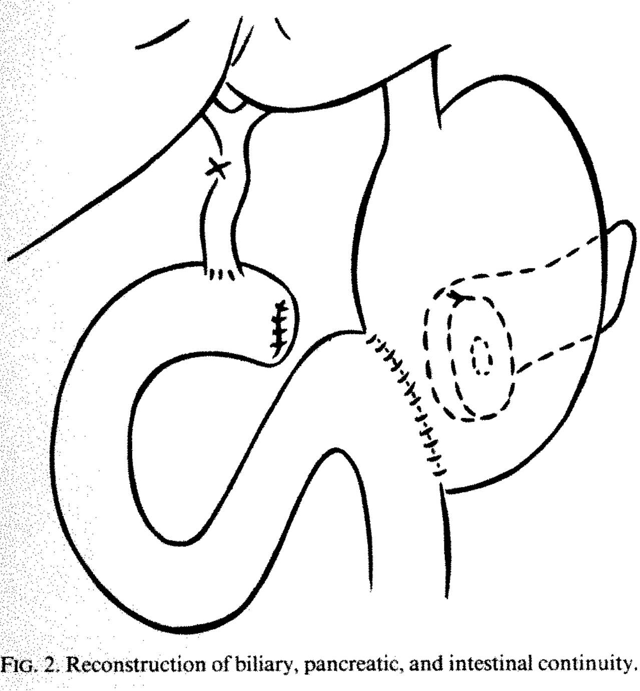

FIG. 2. Reconstruction of biliary, pancreatic, and intestinal continuity.

Thus, morbidity rates in relation to the pancreaticogastrostomy may perhaps be attributed to this gastrointestinal bleeding. The average postoperative hospital stay was 15 ± 3 days. Periodic clinical evaluations in all patients suggest the permeability of the pancreatic duct because none of the patients presented with symptoms of pancreatic insufficiency. One patient (chronic pancreatitis) had two recurrent anastomotic ulcers (after 12 and 20 months, respectively), which necessitated two successive degastrogastrostomies and truncal vagotomies (the latter were performed by left thoracotomy). Three out of 11 patients with malignant tumors died 13, 24, and 50 months after the operation, respectively, and postmortem examination confirmed the permeability of the pancreatic duct.

Discussion

On the basis of experimental studies on dogs carried out by Tripodi and Sherwin in 1934[18] and then by Person and Glenn in 1939,[19] which showed evidence of long-term pancreatic secretion after pancreaticogastrostomy, Waugh and Clagett in 1944[8] performed the first human pancreaticogastrostomy. This technique, though rarely used, was reintroduced by Mackie et al.[17] in 1975 and by Reding[20] in 1978.

Our results (no mortality and low morbidity rates without pancreaticogastrostomy leakage) are consistent with data concerning this method of reconstruction published in the literature: cumulative mortality is 4.5% (6 out of 134 patients, including our patients) with only one pancreatic leakage, mentioned by Mackie (Table 1). This single case of pancreatic fistula disappeared after prolonged use of nasogastric aspiration. The main complication appears to be pancreatic anastomosis bleeding in the stomach (4 cases out of 136 patients); thus, we recommend careful hemostasis of the pancreaticogastric anastomosis.

Pancreaticogastrostomy presents the following advantages:

1. It is a simple method of reconstruction because the pancreas lies in natural apposition to the posterior wall of the stomach, and so the anastomosis is easy to accomplish technically without tension.
2. The very low incidence of pancreatitis and pancreatic fistula is probably a consequence of trypsine neutralization by gastric acidity.

TABLE 1. *Operative Mortality Rates and Nonlethal Complications Reported for Pancreaticogastrostomy after Radical Pancreatoduodenectomy*

Reference	Year	No. of Cases	Operative Deaths	Cause of Death	% Operative Mortality Rate	Death Related to Anastomotic Leak	Nonfatal Complications
Waugh and Clagett[8]	1946	1	0	0	0	—	—
Wells et al.[9]	1952	3	1	Pulmonary Infection	33	—	—
Dill-Russel[10]	1952	2	1	Biliary péritonitis	50	—	—
Ingebrigtsen and Langfeldt[11]	1952	2	0	—	0	—	—
Sames[12]	1952	1	0	—	0	—	—
Nanson[13]	1954	1	0	—	0	—	—
Silverstone[14]	1956	1	0	—	0	—	—
Millbourn[15]	1959	7	0	—	0	—	—
Pataky and Popik[16]	1959	1	0	—	0	—	—
Mackie, Rhodes, and Park[17]	1975	25	2	Pancreatic abcess Biliary fistula	8	1	2 Biliary fistulas 1 Transitory pancreatic fistula nonoperated
Reding[20]	1978	6	0	—	0	—	
Telford and Mason[21]	1981	9	0	0	0	—	
Flautner et al.[24] *	1985	27	0	0	0	0	2 Biliary fistulas 1 Pancreatic anastomosis bleeding nonoperated
Kapur[30]	1986	31	2	Peritoneal bleeding Unexplained death	6.4	—	1 Biliary fistula 1 Bleeding nonoperated 1 Pancreatic anastomosis bleeding operated 4 Pulmonary infections
Our patients	1987	17	0	0	0	—	1 Peritoneal bleeding 1 Intestinal bleeding
Total		134	6	—	4.5	1	15

* Pylorus preservation.

Other probable contributing factors are the possibility of nasogastric aspiration on contact with the anastomosis; and the absence of a long jejunal loop where pancreatic and biliary secretions can accumulate, increasing intraluminal pressure and loop weight. Furthermore, the significant distance between pancreatic and biliary anastomosis prevents, in the event of leakage of one of these anastomosis, deleterious effects on the other.

Telescoping the pancreatic stump into the posterior wall of the stomach[17] or performing mucosa-to-mucosa anastomosis[21] have been proposed. Nevertheless, in our opinion, none of these technical modifications seems necessary. Radiologic and endoscopic access to pancreaticogastrostomy is simple, allowing long-term evaluation of the permeability of the anastomosis and of the amount of pancreatic enzymes. Thus, Millbourn[15] successfully reperformed reanastomosis because of an obliterated duct discovered 2 years and 3 months after initial pancreaticogastrostomy. Current progress in endoscopic surgery would probably prevent the necessity of such a reoperation.

To prevent anastomotic peptic ulceration and weight loss, pylorus preservation has been recommended primarily in chronic pancreatitis.[22,23] This pylorus preservation can be performed with pancreaticogastrostomy, as Flautner et al.[24] have reported. The almost unanimously reported positive results after pancreaticogastrostomy are comparable with the best results reported after pancreatojejunal anastomosis in most recent series.[4,25–29]

In conclusion, this method of reconstruction merits widespread utilization due to its simplicity and safety.

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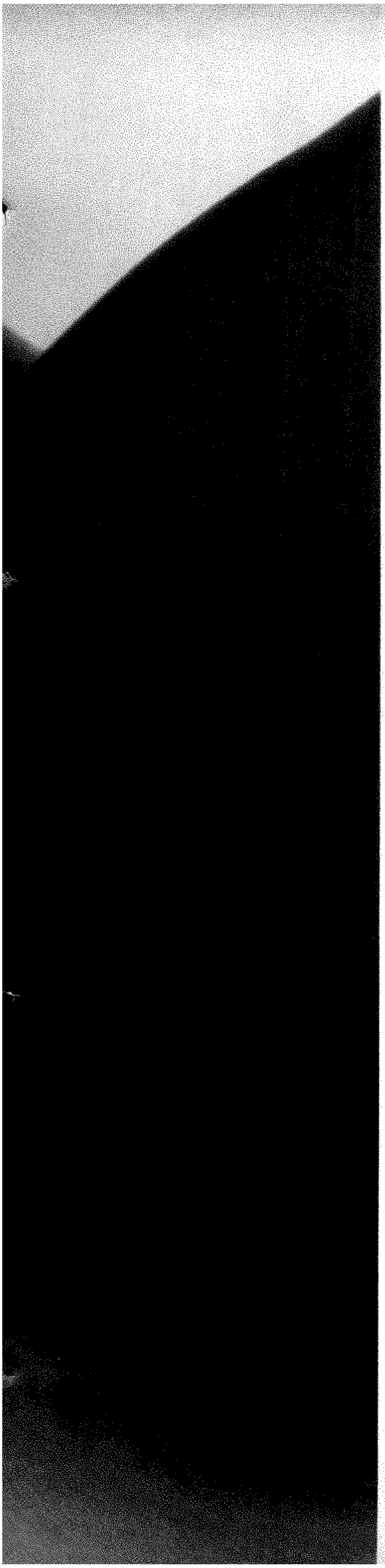

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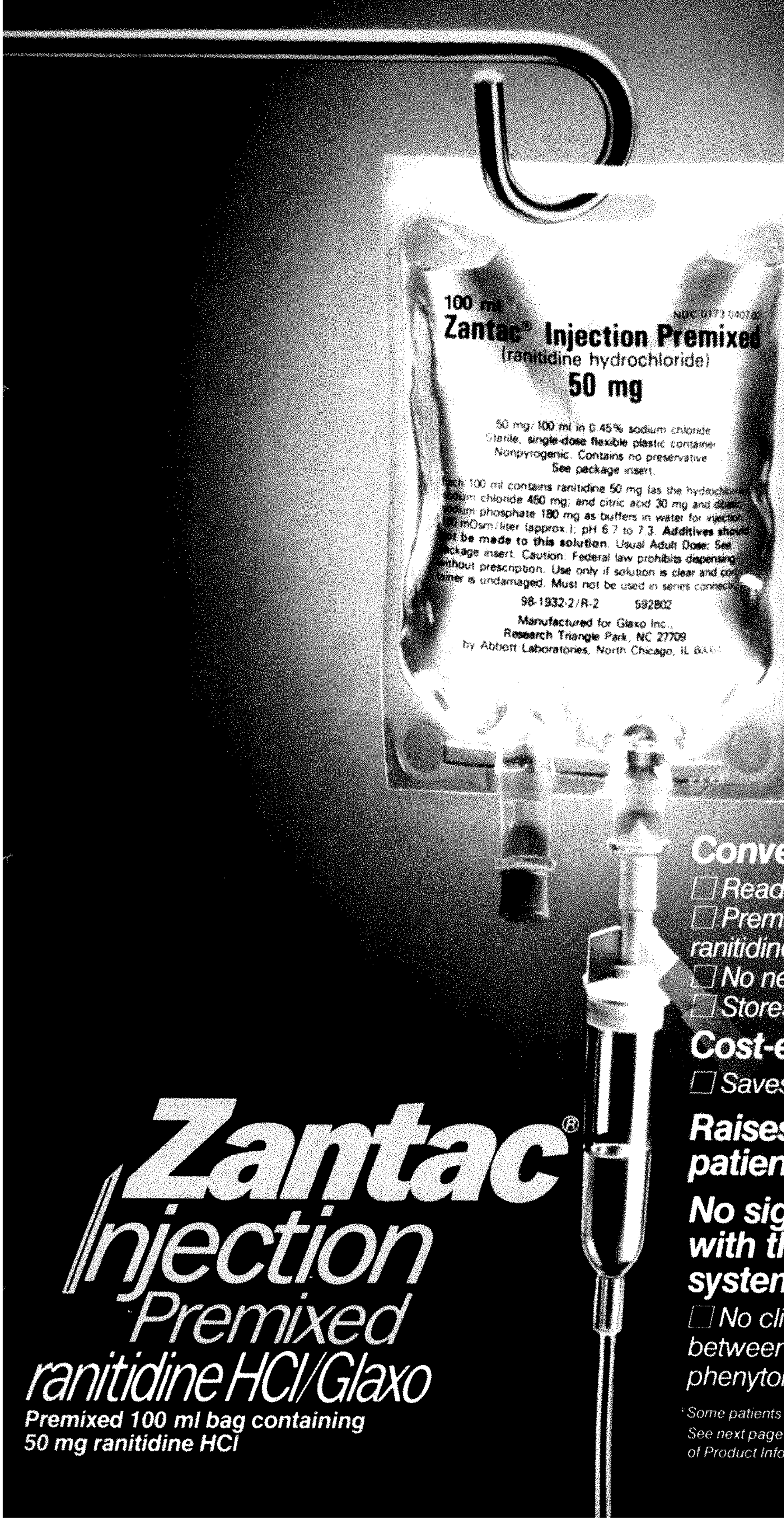
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Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.
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Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.
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Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.
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Pancreatitis in Childhood

Experience with 49 Patients

DANIEL W. ZIEGLER, M.D., JULIE A. LONG, M.D., ARVIN I. PHILIPPART, M.D., and MICHAEL D. KLEIN, M.D.

Pancreatitis in children is not common but can be associated with severe morbidity rates. We have treated 49 children with pancreatitis over the past 12 years ranging in age from 1 month to 18 years. One third of the patients had biliary tract disease as an etiology, with nearly half of these being related to underlying hematologic disease, usually sickle cell anemia. Another third of the pancreatitis was due to trauma, and one third of these were related to child abuse. Other etologies were systemic disease (6 patients), congenital anomalies (8 patients), and idiopathic (3 cases). Eighty-two per cent of the patients presented with abdominal pain, but four children, all less than 4 years old, presented with an abdominal mass. Twenty-nine patients required 33 operations for pancreatitis. Fifteen of the 16 patients with biliary tract disease and all patients with congenital anomalies required operation. Six of the 16 patients with trauma required operation and none of those with systemic disease. As in adults ultrasonographic examination and CT scan are most important in the diagnosis; medical treatment consists of intravenous (I.V.) fluids, nasogastric suction, and total parenteral nutrition (TPN), and risk factors can help predict the severity of the disease while amylase alone is not related to severity. Different from adults, in children an etiology can usually be determined. The common etiologies, biliary tract disease, trauma, and congenital anomalies frequently require operation.

PANCREATITIS in children is not common but can be associated with severe morbidity rates. Mortality rates range from 0–78%.[1-5] In most series, the etiology of pancreatitis in childhood is either trauma or unknown.[1,2,4] We treated 49 children over a 12-year period at a single institution. Biliary tract disease emerged as a frequent cause of pancreatitis, and a diligent search for the cause of pancreatitis was successful in 94% of the cases.

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Materials and Methods

The records of 49 patients with the diagnosis of pancreatitis hospitalized at the Children's Hospital of Michigan between 1974 and 1986 were reviewed. The criteria for diagnosis were amylase measurements in 27 patients (serum amylase greater than 200 IU/dL/24 h or urine amylase greater than 300 IU/24 h) and intraoperative pathology consistent with pancreatitis in 22 patients.

Results

These 49 patients ranged in age from 1 month to 18 years and included 27 males and 22 females (Table 1). Trauma accounted for 33% of the cases of pancreatitis. Nonmotorized vehicles were associated with five cases whereas motor vehicles contributed to three cases. In five cases (10% of the series) child abuse was the etiology. The average age of these children was younger than any other group (including congenital anomalies) presenting at 27 months. Other blunt trauma caused three cases. No case of pancreatitis was associated with penetrating trauma in this series.

Sixteen patients had pancreatitis associated with biliary tract disease. The most common etiology was sickle cell anemia (six patients). All of the patients with sickle cell disease had multiple admissions for abdominal pain with some episodes not typical for sickle cell crisis. Eight patients without sickle cell disease also had cholelithiasis. Three had no predisposing factors for gallstones and five did. One had morbid obesity, 1 was using corticosteroids for a kidney transplant, 1 had cryptogenic cirrhosis, 1 had G-6-PD deficiency, and 1 had hemolytic-ure-

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TABLE 1. *Etiology, Age, and Sex Distribution of Children with Pancreatitis*

Etiology	No. of Patients (%)	Mean Age (yr) (Range)	Male:Female Ratio
Biliary tract (ALL)	16 (33)	12.3 (3.7–18)	7:9
Related to hematologic disease	7 (14)	12 (9–17)	4:3
Trauma	16 (33)	5.7 (0.3–13.8)	3:1
Systemic disease	6 (12)	10.8 (4–15)	5:1
Congenital anomalies	8 (16)	5.9 (0.08–14)	1:3
Idiopathic	3 (6)	14.3 (12–16)	3:0
Total	49	10.6 (0.08–18)	27:22

mic syndrome. Two patients had biliary tract disease without sickle cell anemia or cholelithiasis. One had already had a cholecystectomy at another hospital, and the other had a dilated common hepatic duct and common bile duct on endoscopic retrograde cannulation of the pancreatic duct (ERCP) without stones or stricture raising the question of prior passage of a gallstone.

Of the six patients with an underlying systemic disease, one had mumps encephalitis and five had diabetes mellitus (including one patient who also had cystic fibrosis). The congenital anomalies included four anomalies of the biliary and pancreatic ducts, a gastric duplication cyst, two choledochal cysts, and a pancreatic cystadenoma associated with cytomegalovirus infection. The four ductal anomalies included a pancreas divisum, pancreatic ductal cyst, atresia of the duct of Wirsung with stenosis of the duct of Santorini and separate common bile duct entrance, and a duodenal diverticulum associated with dilated bile ducts and an ectopic sphincter of Oddi.

Three patients remained without an apparent etiology for their pancreatitis. In two of these cases the clinical course was mild, and in one it was protracted. Forty of 49 patients (82%) presented with abdominal pain. The pain was described as generalized in six, epigastric in 11, and right upper quadrant in 16. One had radiation of pain to the back. Twenty-six patients presented with vomiting and three had vomiting with no abdominal pain. Four children, all less than 4 years old, presented with an abdominal mass without pain. Additional findings were fever in 6 patients, abdominal distention in 18 patients, jaundice in 3 patients, and pleural effusion in 1 patient.

TABLE 2. *Relationship of Age to Presenting Signs and Symptoms*

	Age (yr)			
	0–5 (N = 15)	5–10 (N = 13)	10–18 (N = 21)	Total
Pain	10 (67)	11 (85)	19 (90)	40 (82)
Vomiting	8 (53)	7 (54)	11 (52)	26 (53)
Mass	5 (33)	0	3 (15)	8 (16)
Fever	2 (14)	2 (15)	1 (5)	5 (10)
Distention	9 (64)	3 (23)	6 (30)	18 (37)
Other	0	7 (54)	2 (10)	9 (18)

Percentages are given in parentheses.

The relationship of age to signs and symptoms is presented in Table 2. Younger patients often presented without pain and were more likely to have abdominal distension. Forty-two patients had plain films of the abdomen and 23 (55%) had abnormal findings. Five patients had calcifications in the area of the pancreas and 14 had a pattern of ileus. The other three revealed evidence of a mass effect in the upper abdomen. Twenty-four patients had an upper gastrointestinal (UGI) series. This was abnormal in ten, with three patients demonstrating displacement of the duodenum.

Thirty-four patients had ultrasonography and 12 had a CT scan. The ultrasonographic examination demonstrated a pancreatic mass in 10 and an enlarged pancreas in 13. In nine patients, the pancreas could not be specifically identified. The CT scan demonstrated a pancreatic mass in 6, an enlarged pancreas in 9, and a normal pancreas in 2. There was no age correlation with ability to image the pancreas by ultrasound.

Fifteen of the 49 patients had a pancreatic mass detected by physical examination or some imaging technique. Eight of these were pseudocysts, 1 was a duplication cyst, 4 were congenital cysts, and 2 were pancreatic abscesses. Thirteen of 15 patients with a mass had an ultrasonographic examination. The ultrasonographic examination demonstrated the mass in ten patients. In one patient with a duplication cyst, the ultrasound did not demonstrate the mass but it was demonstrated on CT scan.

We used ERCP in three of our patients to evaluate recurrent pancreatitis. The ERCP established a diagnosis of pancreas divisum in one patient. One patient had a fibrosed pancreatic duct, and the third was normal. In no case did the ERCP cause an exacerbation of pancreatitis.

We retrospectively graded the severity of pancreatitis in this series using Imrie's modification of Ranson and Pasternack's criteria.[6,7] The ten factors utilized and the frequency of their occurrence are listed in Table 3. In contrast to Ranson's criteria this study excluded age at admission, history of previous episodes, high base deficit, and estimated fluid sequestration because of characteristics unique to a pediatric population or lack of data. In Table 4 the number of positive factors in a patient is related to the amylase level and complications.

TABLE 3. *Risk Factors in Children with Pancreatitis*

Factor	No. of Patients
White count ≥16,000/mm^3	14
Calcium ≤8 mEq/dL	3
Fasting blood sugar ≥200 mg/dL	5
LDH ≥350 IU	3
SGOT ≥250 IU	1
PaO$_2$ ≤60 mmHg	4
Fall in hematocrit of more than 10% in 24 h	2
Rise in BUN more than 5 mg/dL in 24 h	0

TABLE 4. *Correlation of Risk Factors and Amylase with Complications in Children with Pancreatitis*

No. of Factors	No. of Patients	Average Amylase Level	Complications	%
0	25	1038	5 Recurrences	20
			2 Pseudocysts	8
1	19	1229	2 Recurrences	10
			4 Pseudocysts	21
2	1	913	0 Recurrences	0
			2 Pseudocysts	0
3	1	918	0 Recurrences	0
			1 Mortality	100
4	3	2972	3 Recurrences	100
			1 Pseudocyst	33
			2 Pancreatic abscesses	67

Fourteen patients were treated with I.V. fluids and no oral intake. Six of these patients required an operation during their hospitalization. Seventeen patients were initially treated with I.V. fluids and nasogastric suction. Eleven required surgery. Eighteen patients were treated with I.V. fluids, nasogastric suction, and hyperalimentation. Twelve required operations.

A total of 29 patients (59%) required operation (Table 5), and four required reoperation for complications or continued pancreatitis. Fifteen of 16 patients with biliary tract disease had operative procedures. Each of these patients had cholecystectomy, 12 with cholangiography including four with common bile duct explorations. The majority of these procedures were performed following typical episodes of gallstone pancreatitis. Six patients with sickle cell anemia were treated medically for the acute attack, and five underwent exchange transfusion followed by cholecystectomy with no postoperative recurrence. One patient developed recurrent pancreatitis following cholecystectomy, and subsequent evaluation failed to reveal an etiology. There was not one mortality in the surgically treated group.

Five of the operated patients developed recurrences. Three patients required more extensive procedures: 1 cholecystectomy with duodenotomy and Roux-en-Y choledochojejunostomy, 1 cholecystectomy with external drainage of a pseudocyst, and 1 cholecystectomy with pancreatic cystogastrostomy. Six of 16 patients with traumatic pancreatitis required operation. One patient initially operated on at an outside hospital required reoperation to drain an abscess. The other five patients all had drainage of fluid collections: 2 laparotomies with drainage of the lesser sac, 1 cystogastrostomy, 1 Roux-en-Y pancreatic cystojejunostomy, and 1 external drainage of pseudocyst with jejunal resection. One patient with percutaneous drainage of the pseudocyst was spared laparotomy but required 2 months of further hospitalization.

All eight patients with congential anomalies had operative procedures. One patient with an ectopic sphincter was treated with cholecystectomy and transduodenal sphincterotomy. A case of gastric duplication underwent distal pancreatectomy, resection of jejunum, and gastric duplication. An infant with a cystadenoma and cytomegalovirus infection had excision of cystadenoma. A patient with pancreatic cyst was treated with resection of the tail of the pancreas. A patient with stenosis of the duct of Santorini and atresia of the duct of Wirsung delineated by intraoperative pancreatogram had cholecystectomy with common bile duct exploration and transduodenal sphincteroplasty. One case of pancreas divisum was treated with cholecystectomy, pancreatogram, and Santorini sphincteroplasty. This patient required a Roux-en-Y pancreatic cystojejunostomy revision. Two choledochal cysts were treated by resection and Roux-en-Y choledochojejunostomy.

None of the six patients with systemic disease and pancreatitis required operation. One of three patients with idiopathic pancreatitis underwent exploratory laparotomy and external drainage of a pancreatic pseudocyst. Morbidity other than recurrence occurred in ten patients. Six required ventilatory support. One patient had a cardiac arrest from hypercalcemia. One patient

TABLE 5. *Operative Treatment of Pancreatitis in Children*

Etiology	No. of Patients	No. Operated	Recurrence
Biliary tract	16	14	—
Hematologic disease	7	6	0
Other	9	8	3
Trauma	16	6	1
Congenital anomalies	8	8	1
Systemic disease	6	0	0
Idiopathic	3	0	0
Total	49	29	5 (18)

had intractable seizures requiring phenobarbital coma. One patient with sickle cell anemia developed respiratory distress after an exchange transfusion. One patient had respiratory failure with sepsis. Two patients with severe pancreatitis presented with shock and respiratory failure.

Discussion

Although pancreatitis is uncommon in childhood, it should be suspected in children with abdominal complaints. Not all children with pancreatitis present with abdominal pain. In this series seven patients (16%) presented with vomiting and four (9%) presented with an abdominal mass. Other patients without significant pain presented with fever, abdominal distention, jaundice, pleural effusion, and Grey Turner's sign.

Ultrasound is very useful in the diagnosis of pancreatitis in childhood. If a diagnosis can be made with ultrasound alone, one can avoid the more expensive CT with its higher radiation. All the pseudocysts in our patients were detected by ultrasound. The usefulness of the ultrasound suffers because it cannot always visualize the pancreas. The pancreas was not visualized in 25% of our examinations. Despite common wisdom that children have less retroperitoneal fat and therefore their pancreas is difficult to visualize, the CT scan was able to visualize the pancreas in all our patients studied.[8] While ERCP was used infrequently in this series, we agree with O'Neill that it is a major tool for evaluating chronic pancreatitis and planning ductal reconstruction.[9]

The presenting age of the patient can point to the etiology of pancreatitis. While trauma is a frequent cause of pancreatitis at any age, it was the most common etiology in the youngest patients in this series. In all patients under 4 years of age, pancreatitis was caused by congenital anomalies or trauma. No history of trauma may be given in an abused infant presenting with abdominal symptoms.[10] Child abuse was responsible for a significant proportion of the cases (10%) with an average age of 27 months. Our approach, therefore, is to aggressively search for congenital anomalies and exclude child abuse in this age group.

Risk factors did help predict who would develop complications. As in adults, elevated amylase alone is not an independent risk factor for predicting severity of pancreatitis. Of 45 patients with zero to two risk factors, 6 (13%) developed a pseudocyst and 7 (16%) developed recurrent pancreatitis. Of the four patients with three or four risk factors, 1 (25%) developed pseudocyst, 2 developed abscesses (50%) and 3 (75%) developed recurrent pancreatitis. Most of the complications and the only mortality occurred in the group with three or four risk factors.

The initial treatment of pancreatitis in children includes I.V. fluids and nasogastric suction. Antibiotics are used only when there is evidence of infection. Patients with two or more risk factors warrant closer observation. Thirty per cent of our patients were successfully treated with either I.V. fluids alone or I.V. fluids and nasogastric suction. In general, enteral feeding can be started once abdominal pain has subsided and the amylase is returning to normal.

Two pediatric series with a 10–12% overall incidence of pseudocyst had a 30% incidence of traumatic pancreatitis.[1,11] Pseudocysts occurred in 17% of our cases but in 38% of our cases of traumatic pancreatitis. About 20% of pancreatic pseudocysts can be expected to resolve spontaneously.[12] Three of our patients (37%) had spontaneous resolution of the pseudocyst. While percutaneous drainage of a pseudocyst appeared to prolong the course of one of our patients, it is an option allowing stabilization of a septic patient prior to definitive surgery.

In three of our patients, steroids may have played a role in the development of pancreatitis. All of these patients had a prolonged hospitalization with complications of sepsis, respiratory, and renal failure. Although steroids have not been directly implicated in causing pancreatitis, the mortality rate in steroid-associated pancreatitis is reported to be about 50% with nonlethal underlying disease.[13,14] Close monitoring and early treatment is certainly warranted in patients administered steroids suspected of having pancreatitis.

Thirty-three per cent of our patients had pancreatitis secondary to acquired biliary tract disease. Blumenstock et al., in reviewing 36 cases of pancreatitis, cited biliary tract disease as an infrequent cause. Others report biliary tract disease as a cause in 0–24% of cases.[1-5,16] The higher incidence in this series is partially explained by the incidence of sickle cell anemia. Eight patients, however, had biliary tract disease causing pancreatitis without associated hematologic abnormalities. Two of the 14 patients (14%) with gallstone pancreatitis developed a recurrence before elective surgery was done. While this is lower than the 37% rate reported for adults, to prevent recurrences, we now recommend cholecystectomy during the initial hospitalization for gallstone pancreatitis.[17,18]

This large series of patients with pancreatitis from a single children's hospital emphasizes the similarities and differences of pancreatitis in children and adults. Aggressive diagnostic evaluation reveals a cause in 94% of cases. While it is unusual for patients with systemic disease and unknown etiology to require operative therapy, it is common for patients with traumatic pancreatitis and biliary tract disease to require operation. Operative therapy is necessary for congenital anomalies to avoid recurrent disease. The risk factors for severity of disease applied to adult populations are also useful in predicting morbidity and mortality rates in pediatric populations. The low mortality rate in this series may be due to early diagnosis and surgical intervention.

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Surgical Oncology Research

A Disappointing Status Report

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The purpose of this paper is to evaluate certain aspects of the present status of surgical oncology research. We have attempted to define the magnitude of the problem, characterize features unique to the surgical community, and formulate potential solutions. Demographic data concerning grant applications submitted to and funded by the National Cancer Institute (NCI) over the time period from 1980 to 1985 were analyzed. Departments of surgery submitted and were awarded substantially fewer grants over the study period than departments of medicine. Additionally, the number of applications submitted from departments of medicine increased during this time period while those from departments of surgery declined. This record is particularly worrisome because it occurred during a period of time of unprecedented scientific and educational opportunities and support mechanisms provided by the NCI. Further conclusions and potential solutions are discussed in this paper.

THE NATIONAL CANCER INSTITUTE (NCI) is committed to supporting the broadest possible participation in the national research effort to elucidate the biology of and identify superior therapy for malignant diseases. In this regard, the surgical community has been actively encouraged to pursue both basic and clinical research questions. Such encouragement is a natural extension of the historically important role of surgeons as cancer investigators as well as their central role in cancer management. Consequently, over the past 8 years the Division of Cancer Treatment of the NCI has sponsored 20 separate initiatives targeted to fostering more and better surgical oncology research.

However, despite the major involvement of surgeons in the care of cancer patients, concerns of insufficient access to research support have been voiced by a variety of individual surgical investigators. Frustrated by a perceived inability to successfully compete for NCI grant support, some surgical oncologists have criticized aspects of the current NCI peer-review mechanisms of awarding grants. Because of these serious concerns, we have undertaken a study to define the magnitude of the problem, characterize features unique to the surgical community, and formulate potential solutions.

Methods

Demographic data concerning grant applications submitted and funded from a recent time period have been analyzed. This information was provided by the Division of Research Grants of the National Institutes of Health (NIH). The data were restricted to applications submitted from various clinical departments of medical schools because the Division of Research Grants' system of data collection provides information by departments only for medical schools in the United States. Therefore, other institutions such as free-standing cancer centers and non-medical school research institutes could not be considered in this paper.

Data were collected from the years 1980–1985 in order to focus on recent trends. Grant submissions were designated according to the medical school department appointment of the principal investigator. The specialty departments evaluated were: medicine, obstetrics and gynecology, radiology, pediatrics, and surgery. There is an *other* category, which includes all of the clinical departments not specifically listed above. These are listed in Table 1. Two surgical subspecialties, which had their own department codes, otorhinolaryngology and orthopedic surgery, were included with surgery. It is possible

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TABLE 1. *Clinical Departments in Other Category*

Total Submissions (1980–1985)	Departments
4	Anesthesiology
69	Dermatology
72	Family practice
37	Neurology
15	Ophthalmology
1	Physical medicine and rehabilitation
42	Psychiatry
538	Public health and preventive medicine
32	Other clinical sciences

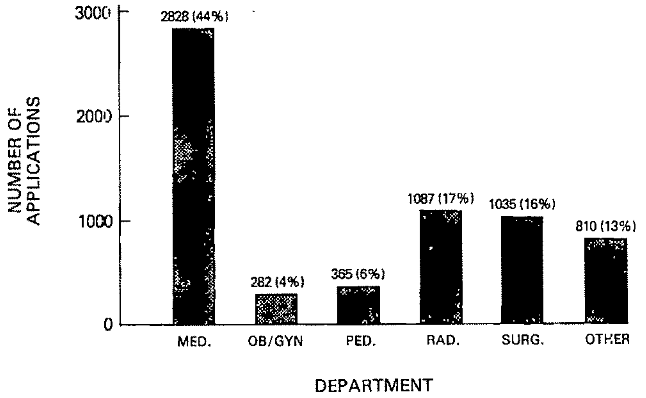

FIG. 1. Number of clinical applications submitted by department: 1980–1985 (National Cancer Institute).

that some grant applications were submitted by surgeons through nonsurgical departments; however, we had no way of reliably identifying such submissions. With this data base, we were able to determine numbers of applications submitted, numbers recommended for award, numbers of grants actually awarded, and the success rates (defined as the number of grants awarded divided by number of applications submitted). Comparisons of success rates by department were performed for individual years and for the entire time interval considered using a chi square test corrected for continuity. No attempt was made to differentiate between the types of grants submitted; *e.g.*, RO1, PO1, KO8, *etc.* Likewise, we did not distinguish as to whether the principal investigator held an M.D., Ph.D., or M.D.-Ph.D. degree, nor did we perform analyses based upon the study section to which an application was submitted. These data are available and will form the basis of a subsequent analysis. To place the information concerning the NCI in proper perspective, these data were compared to similar data obtained relative to the NIH as a whole.

Results

For the six most recent years where data were complete, there was a total of 6407 applications submitted. As shown in Figure 1, 44% of the applications were submitted from departments of medicine, 17% from departments of radiology, 16% from departments of surgery, 4% from departments of obstetrics and gynecology, and 6% from departments of pediatrics. Thus, there were nearly three times as many grants submitted from departments of medicine as from departments of surgery. In Figure 2 the overall success rate by department is presented. The success of applications submitted from departments of medicine, pediatrics, and radiology had comparable award rates varying from 34–36%. However, grants submitted from departments of surgery and obstetrics and gynecology were less successful by approximately 10 percentage points. Thus, comparing surgery and medicine, there are not only many more applications being submitted from departments of medicine, their success rate is substantially and significantly higher ($p < 0.001$, chi square test).

In order to determine if trends could be identified, the data were analyzed by individual year. Figure 3 depicts numbers of grants submitted by department from the year 1980 and the year 1985. The only departments with fewer submissions in 1985 than in 1980 were surgery and OB/GYN. The number of grants submitted from departments of medicine increased by 55% (363 to 566) while grants submitted from departments of surgery declined by 17% (203 to 168). Figure 4 depicts the success rate by department for 1980 and 1985. The success rate for all departments decreased to a variable extent. The proportional decreases in success rates were more extreme for departments of surgery and OB/GYN than for departments of medicine. To demonstrate that the 1985 data are truly reflective of at least a short-term trend, data are displayed year-by-year during this interval in Figures 5 and 6. In Figure 5 we show data on submissions as a percentage of the number of applications sub-

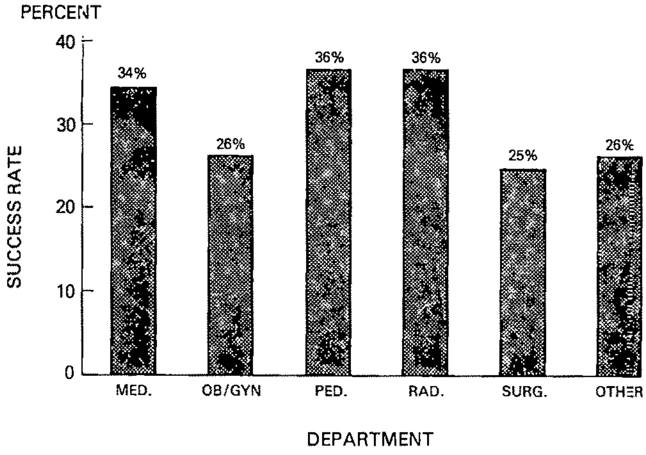

FIG. 2. Success rate (awarded/submitted) of clinical applications by department: 1980–1985 (National Cancer Institute).

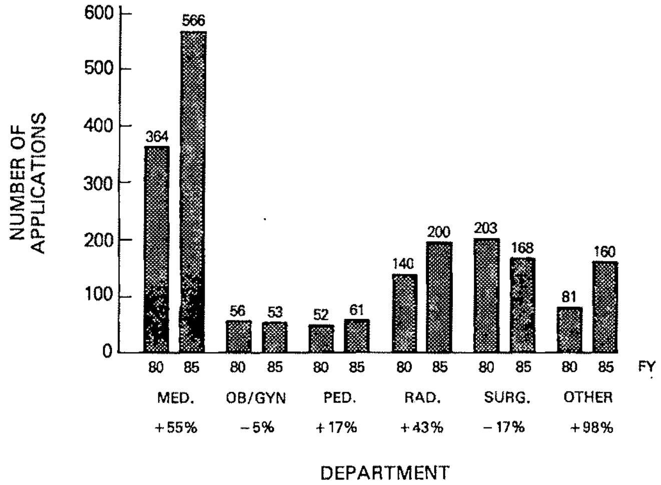

FIG. 3. Number of clinical applications submitted by department: 1980 and 1985 (National Cancer Institute).

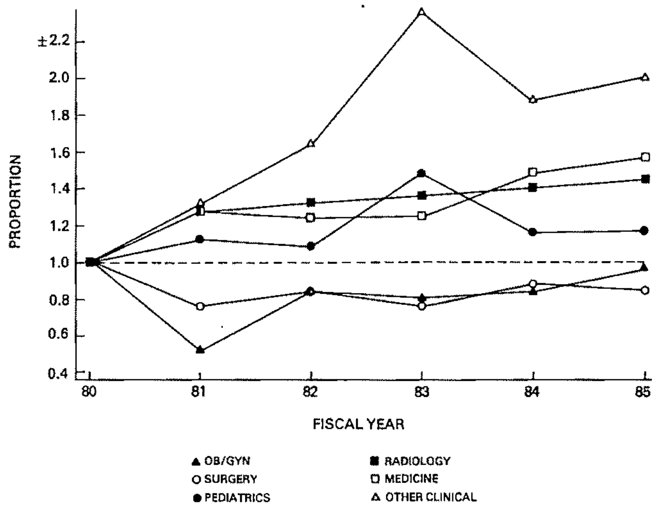

FIG. 5. Trends in number of applications, by department and fiscal year: 1980–1985 (National Cancer Institute).

mitted in 1980, the *baseline* year for this report. The dotted line represents the level of submissions in 1980. As shown, surgery and OB/GYN demonstrated a downward trend (consistently fewer submissions than in 1980) while all other departments have increased their number of applications. Figure 6 shows the year-by-year success rates for the same time interval. While the general pattern is similar for all departments, the success rates for applications from departments of surgery and OB/GYN remain fairly consistently at or near the bottom.

In order to place the data from the NCI into a broader perspective, the data were analyzed relative to the NIH overall trends. Between the years 1980 and 1985, a total of 32,045 applications were submitted by clinical departments. Forty-three per cent of the grants were submitted from departments of medicine, 11% were submitted from departments of pediatrics, 13% from departments of surgery, 6% from departments of radiology, and 5% from departments of OB/GYN (Fig. 7). For departments of surgery and medicine, the patterns within the NCI and the NIH are remarkably similar. Figure 8 displays the success rate by department for the years 1980 to 1985. Again, there is remarkable similarity of the success rates within the NCI and the NIH.

Discussion

The analyses presented in this paper are limited and should not be overinterpreted. The data base is restricted only to university medical schools and does not take into consideration many other institutions supported in part by the NCI. Also, it is not possible to describe specific surgery subspecialties; thus some sub-

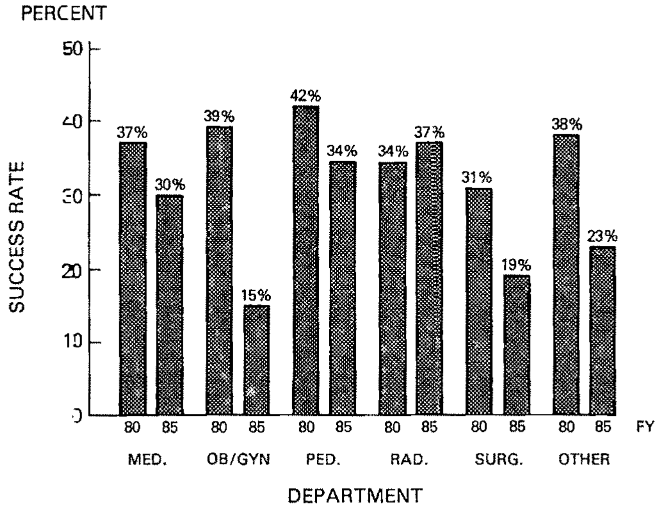

FIG. 4. Success rate (awarded/submitted) of clinical applications by department: 1980 and 1985 (National Cancer Institute).

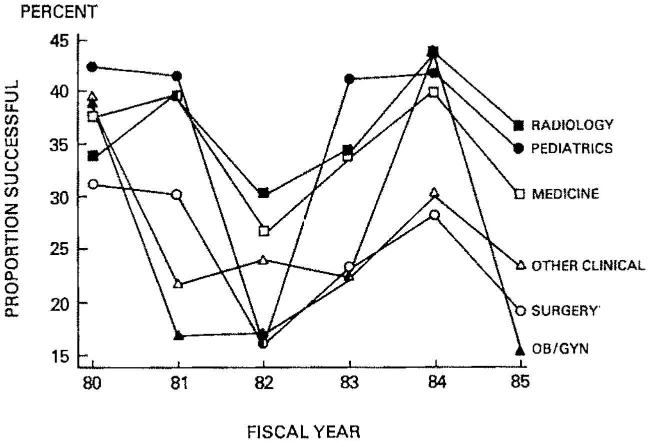

FIG. 6. Proportion of successful applications, by department and fiscal year: 1980–1985 (National Cancer Institute).

specialties may be faring significantly better than others. Additionally, not all cancer-related applications are submitted to the NCI, although the majority are.

The data trends for surgical oncology are disappointing. Departments of surgery have submitted and have been awarded substantially fewer grants over the last 6 years than departments of medicine. In addition, the number of applications submitted from departments of medicine has increased while departments of surgery have submitted fewer grants over the past 6 years. This overall lack of expansion is worrisome because it has taken place in the face of unprecedented scientific and educational opportunities and support mechanisms provided by the Division of Cancer Treatment (DCT) and the Division of Cancer Prevention and Control (DCPC) of the NCI. These NCI initiatives have included the acceptance by DCT of the responsibility for surgical oncology extramural activities as well as the creation of a surgery section in the Clinical Investigations Branch of the Cancer Therapy Evaluation Program. The Surgical Oncology Research Development Subcommittee of the DCT Board of Scientific Counselors has been established, and there have been a number of scientific workshops held. Two major training programs have been instituted by DCPC in conjunction with DCT, the Surgical Oncology Training Grant (T-32), and the Clinical Investigator Award (K-08). The latter was not developed solely for surgeons, but the surgical community was a primary target of interest. Also, there have been several program announcements and requests for applications for planning of surgical oncology programs and for basic research activities.

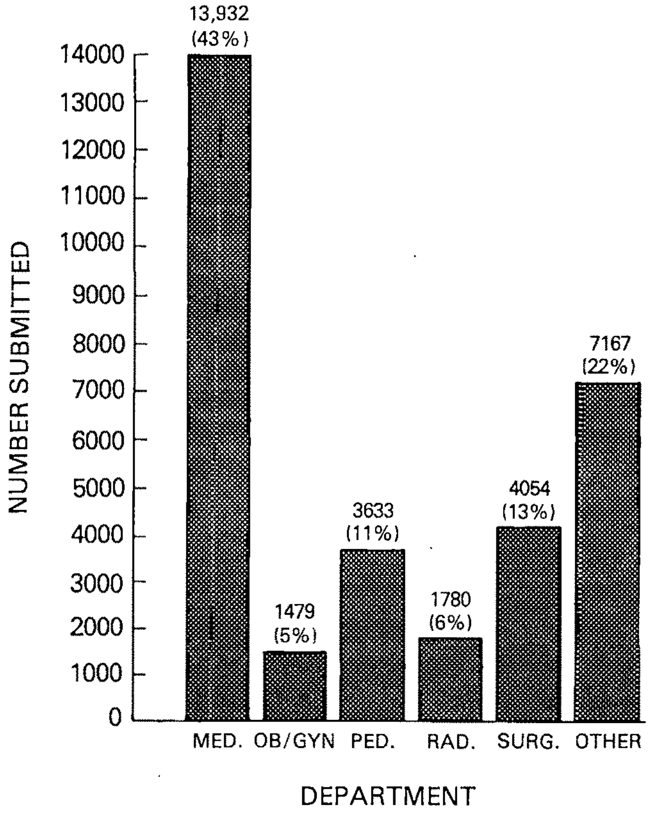

FIG. 7. Number of clinical applications submitted by department: 1980–1985 (National Institute of Health).

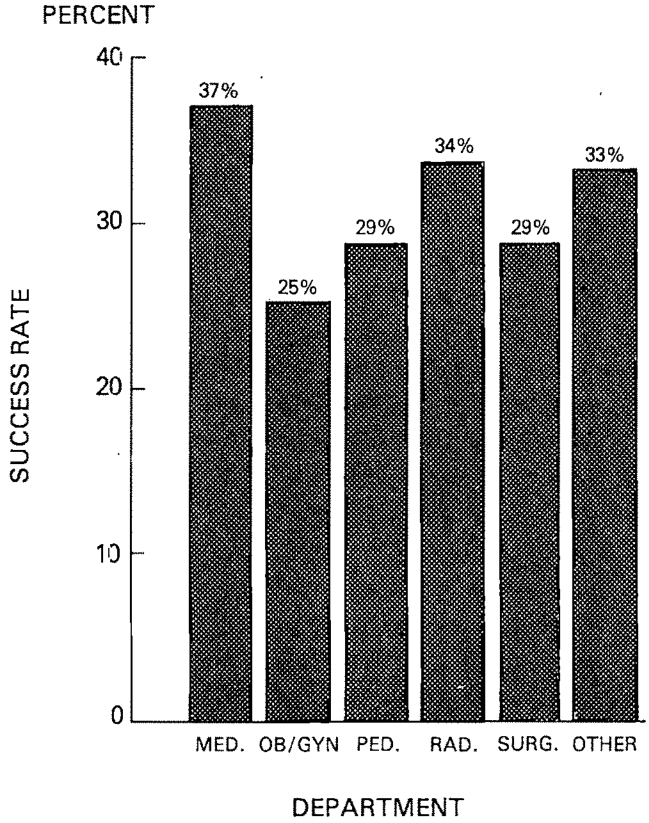

FIG. 8. Success rate (awarded/submitted) of clinical applications by department: 1980–1985 (National Institutes of Health).

A recent publication produced by the Conjoint Council on Surgical Research of the American College of Surgeons is particularly timely and is pertinent to this present analysis.[1] This document consists of reports from six separate committees of special interest including one focusing on cancer. Each committee report includes general observations, opportunities, recommendations, and a summary statement. In addition, appended to this report are two surveys: one conducted by the Society for Academic Surgery and the other by the Society of University Surgeons. Taking this report and the two appended surveys in sum, it would appear that there are some common concerns for the academic surgical community. These include an insufficient number of educational and training opportunities for aspiring academic surgeons; a need to have more protected time allotted for investigators to perform their research; a need for funding sources in addition to those that can be provided by the NIH; an apparent lack of peer recognition of the importance of research and the individual investigator at academic centers; and a perceived need for special study sections to review NIH grant applications.

The solutions to the concerns as outlined both in the Conjoint Council on Surgery Research report, the two appended surveys, and the present study seem fairly obvious. However, the implementation of the solutions may be much more difficult. The NCI has already addressed in part the problem of insufficient education and training opportunities for aspiring academic surgical oncologists. As mentioned earlier, the Surgical Oncology Research Training Grant (SORTG) and the Clinical Investigator Award (CIA) have been created. It is of interest that approximately 13 SORTG applications have been submitted and three have been funded. For a first year effort this is promising. Three CIAs have been awarded. However, in order to award these three grants to surgeons, they were funded out of order according to the payline and as special exceptions.

The need for special study sections constituted to review surgical grant applications has not been well documented but could be investigated further. However, there are two significant problems. Constituting study sections that can adequately review surgical grant applications would be difficult because of the broad research interests of the surgical community. Additionally, as we have shown, there are so few grants submitted, making special review financially unfeasible and the constitution of the study sections difficult. Nevertheless, the NCI is sensitive to this concern and has constituted a special study section to review SORTG proposals on a yearly basis.

The lack of emphasis on surgically sponsored research in academic centers will have to be addressed by the national surgical community. Surgeons committed to research must be provided with both professional and economic rewards by their institutions. Funds and other space manpower resources must be made available to surgeons to permit them to carry out their research activities. In addition, sufficient time for research must be allotted and protected. This obviously has significant financial implications to the department of surgery, medical school, and hospital because of the surgeon's crucial role as an important generator of revenue. It is clear that the decision to implement these policies with a commitment to their success must be made at the highest levels of leadership within departments of surgery and academic institutions.

There is an obvious need for funding to supplement that which may be provided by the NIH. The American Cancer Society, the National Science Foundation, and other organizations have been very helpful in supporting research in the past. Their programs should be carefully scrutinized for opportunities. In addition to these other sources of funding, it is not unreasonable that departments of surgery retain a greater proportion of their clinical earnings for education, training, and research development.

Our data suggest that insufficient numbers of surgical proposals of high merit are being submitted to the NCI and the NIH. This is probably reflective of an insufficient number of academic surgical oncologists with appropriate training and commitment. The academic surgical oncologists who aspire to have research programs need active support from the leadership in their departments of surgery and medical schools, and their time should be guarded to permit them to perform their research duties, the success of which needs appropriate recognition.

Although currently the overall conditions of surgical oncology research and surgical research in general leaves much to be desired, it is very important to recognize that there are areas of success. Several individual surgical oncologists have taken major leadership roles in basic and clinical investigations, developing integrated research programs, and training some fine academic surgeons. These individuals and institutions deserve considerable credit. Nevertheless, there remains much to be done. The NCI, recognizing the primary role played by surgeons in the treatment of cancer patients, remains committed to fostering the research interests of academic surgical oncologists and supporting appropriate research efforts of the surgical oncology community within the bounds of its capabilities.

Acknowledgments

We would like to acknowledge the assistance of Mr. Robert Moore in extracting the relevant data from the information stored by the Division of Research Grants; and Mr. Meyer Gordon of the Office of Associate Director of CTEP in preparation of computer graphics.

Reference

1. Conjoint Council on Surgical Research Reports of the Commission of Special Interests. Longmire, WA, ed. American College Surgeons. 1986.

Effects of Age and Nutritional Status on Surgical Outcomes in Head and Neck Cancer

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Older and younger malnourished and well-nourished head and neck cancer patients scheduled for surgery were studied. More of the young (75%) compared with the old (58%) underwent curative surgery, and only the old with lower clinical stages of cancer were selected. When data on those undergoing surgery were analyzed in regard to older and younger malnourished and well-nourished men, the malnourished old had the poorest surgical outcomes of any group, with significantly more complications and morbidity rates. The well-nourished old had outcomes that did not differ from younger patients. On further examination, 60% of the young malnourished and only 20% of the old malnourished received preoperative enteral or parenteral nutritional support. Findings suggest that more attention to the needs of the older malnourished patients could improve surgical outcomes.

FIFTY YEARS AGO, most surgeons were cautious about operating on elderly patients in the belief that older age was a surgical risk. There is little doubt that age is still a factor in decisions about surgery and that evaluating operative risk is complex. Although morbidity and mortality rates are often similar in old and young after elective surgery, the risk in emergency surgery is much greater in the elderly than in younger patients.[1,2] Furthermore, coexisting morbidity increases with age. Thus, increased surgical risk with age can be attributed in part to multiple pathology, more advanced disease, and more frequent emergency surgery. At the same time, biologic variability increases with age. Although some elderly are frail, most are not. A positive factor for surgery in older patients is often their age, in that they are survivors who have outlived many of their birth cohorts. Numerous studies have shown that good results can be obtained in operating on the elderly when they are properly managed.

Nutritional and immune status are two interrelated factors known to influence surgical outcomes[3,4]; both of these are related to aging. The elderly are more susceptible than younger individuals to nutritional deficiencies because of age-related physiologic changes as well as psychosocial factors.[5] Furthermore, immune function is thought to decline with age.[6] There is increased frequency of cancer with aging, and nutrition and immunocompetence are also associated with cancer.[7]

Malnutrition is known to be high in head and neck cancer. The present study was undertaken to determine whether surgical outcomes differed by older and younger malnourished and well-nourished patients with head and neck cancer.

Methods

Data are taken from a larger 4-year ongoing study of the relationship of nutritional status to surgical outcomes in head and neck cancer patients. The study was initiated in 1984 in Miami at the VA Medical Center. Men admitted for treatment for squamous cell head and neck cancer to surgical wards were selected for study. A total of 120 men (94%) agreed to participate in the study by signing informed consent.

A research nurse collected information describing age, ethnicity, social class, education, marital status, pack/yr of cigarette smoking, diagnosis of alcoholism in the medical record, symptoms, months since onset of symptoms, type and stage of cancer, prior treatments for cancer, and number of days from admission to surgery. In addition, number of current diagnoses and a measure

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of severity of illness were obtained using the Cumulative Illness Rating Scale.[8]

Nutritional status was measured 2 days before surgery with a 23-item Protein Energy Malnutrition Scale (PEMS).[9] The scale provides four subscores as well as an overall score for degree of malnutrition. The research nurse obtained anthropometric data and provided ratings for the history and physical subscores on the PEMS. The anthropometric score is derived from per cent ideal body weight, per cent weight loss, triceps skinfold measurement, and midarm muscle circumference. The clinical history score is based on four-point ratings for degree of adequate nutritional intake, excessive nutrient losses, increased metabolic needs, and catabolic medications. The physical examination score is based on four-point ratings for degree of cachexia, hepatomegaly/ascites, muscle atrophy, edema, change in hair/nails, and changes in condition of the skin. A 24-hour dietary intake was recorded for calculation of caloric intake, and a 24-hour urine sample, covering the same time, was ordered for analysis so that creatinine height index and nitrogen balance could be computed. The Multitest CMI (Merieux Institute), consisting of seven delayed hypersensitivity skin tests, was given and read 48 hours later. Blood samples were drawn for laboratory tests. The laboratory score on the PEMS is derived from values for serum albumin, hemoglobin, lymphocyte counts, transferrin, retinol-binding proteins, creatinine height index, nitrogen balance, and skin tests. Higher scores indicate more malnutrition.

The day before surgery, between 8:00 and 10:00 A.M. blood samples were drawn in a heparinized syringe from the patients and their matched controls. The immune tests were done by laboratory personnel blind to patient or control status and to rating time. Blood samples were drawn again 3 and 30 days after surgery and the same immune tests repeated. Lymphocyte response in culture to phytohemagglutinin (PHA), concanavalin A (con A), and pokeweed mitogen (PWM) were studied using a fixed number of purified lymphocytes as previously described.[10] All cultures were done in triplicate, with the means calculated and responses expressed as counts per minute (cpm) in the stimulated minus unstimulated cultures, with log transformation of the cpm for statistical analyses. Neutrophil chemotaxis was used to assess migration of PMN cell according to methods described by Maderazo,[11] using a Boyden chamber and filters 13 mm in diameter with 5-μm pores with and without zymosan-activated guinea pig serum. Means of triplicate counts of stimulated minus unstimulated cultures were used as the neutrophil response to chemotaxis.

Data were also collected describing the operative procedure and outcome of surgery. Operative data included type of operation, times for anesthesia and surgery, blood loss, whether surgery was performed by ENT or general services, level of operating surgeon, and type of anesthesia.

After surgery, patients were monitored daily for 30 days or until discharge or death to determine signs of complications. Severity of each complication was rated by a surgeon who reviewed the daily records of the research nurse at the end of 30 days. A list of possible complications was scored for degree of severity on a 0 (none) to 4 (extremely severe) scale. Other outcome data included number of days from surgery to discharge, whether the patients were readmitted within 90 days after surgery, and number of days from discharge to readmission for those readmitted.

Data were analyzed in a 2 × 2 factorial design for ANOVA, in which one factor was age (older × younger) and the other factor was nutritional status (well-nourished × malnourished). Age was stratified by 60 or over (older) and under 60 (younger). The PEMS score was used to define nutritional status with a score of 8 and over meaning malnourished and a score under 8 meaning well-nourished.

Results

Of the 120 men admitted to be evaluated for possible surgery, 65 were in the older age group (mean age: 64; SD, 5) and 55 were in the younger age group (mean age: 44; SD, 6). Only 72 actually underwent curative surgery with more of the younger (75%) than the older (58%) men being operated upon.

Operated Versus Nonoperated

A higher average clinical stage of cancer (3.3) was associated with operating upon the young and with not operating upon the old (interaction effect of age with surgery was $F = 6.8$, $p < 0.01$). Thus, older patients with a higher clinical stage of cancer were not selected for surgery even though their average stage was identical to that of the younger patients undergoing surgery. The exclusion of higher stage cancers in older patients accounts for the fact that clinical stage differed significantly by age ($F = 5.4$, $p < 0.01$), with the old being 2.7 and the young 3.3. Although the older group had a greater number of diagnoses than the younger group (4.9 *vs.* 2.6; $F = 7.8$, $p < 0.01$), number of diagnoses did not discriminate significantly between those who were and were not operated upon (3.3 *vs.* 4.2, with those having surgery having more diagnoses). Severity of illness scores did not differ either by age or having surgery. Degree of malnutrition did not differ by age groups; however, there was a trend toward those who were less well-nourished being excluded from surgery, particularly in the older group, but this was not statistically significant. Prior treatment with radiation did not differ

TABLE 1. *Background Characteristics of Old and Young Malnourished and Well-nourished Patients Undergoing Surgery*

	Groups				*F* Ratios		
	Old		Young				
Variables	Malnourished (N = 22)	Well-nourished (N = 16)	Malnourished (N = 23)	Well-nourished (N = 18)	Old *vs.* Young	Malnourished *vs.* Well-nourished	Age × Nutrition
Black (%)	22	7	43	25	3.7	2.0	0.1
Education (yr)	11	11	11	10	0.3	0.4	0.5
Social class*	3.7	3.9	4.3	4.1	3.4	0.1	0.2
Married (%)	77	47	31	58	1.2	0.1	4.3§
ETOH diagnosis (%)	78	73	81	50	0.3	2.2	1.1
Alcohol use past†	3.4	3.4	3.9	3.3	1.2	2.6	2.4
Alcohol use present†	1.9	2.2	2.7	2.3	1.6	0.1	1.2
No. of medications	1.9	1.3	1.0	1.3	0.8	0.0	1.0
Pack/yr smoking habit	55	77	52	74	0.7	6.1‡	0.1

* Social class was rated 1–5, with higher numbers referring to lower class.

† Alcohol use was rated by patient as 1–4, with 4 being extreme.

‡ $p < 0.01$.

§ $p < 0.05$.

significantly, with about one fourth of all groups operated or not having received radiation. However, none of the older, as compared with 17% of the younger patients, had received prior chemotherapy ($F = 7.2$, $p < 0.01$). Records of each of the patients excluded from surgery were reviewed. In the groups, 22% of the old and 33% of the young were not operated upon because their biopsies indicated unresectable tumors. Also, one patient in each group expired before surgery. The remaining patients were referred for either radiation or chemotherapy as the treatment of choice, except for one patient in each group who selected one of these treatments rather than undergoing extensive surgery. In summary, there were no clear indications as to why fewer of the old than the young were selected for surgery. The remaining results focus upon those patients who had surgery.

Background Characteristics

Table 1 shows characteristics of the sample by age and nutritional status. It can be seen that none of the variables differed significantly at a statistical level by older and younger age of the patients. Pack/years of smoking was significantly higher among the well-nourished compared with the malnourished patients ($p < 0.01$). In addition, less of the malnourished young but more of the malnourished old were currently married ($p < 0.05$).

Symptoms and Types of Cancer

Table 2 shows months from onset of symptoms to diagnosis of cancer, types of symptoms, and types of cancer for the four groups. Older men came in sooner than younger men after onset of symptoms, with an average of about 2.9 months in the old as compared with about 5 months in the young ($p < 0.05$). This, however, may also reflect the lower clinical stage of cancer in the old than in the young who received surgery. More of the young than old had symptoms of trouble swallowing ($p < 0.05$) and weight loss ($p < 0.001$). A number of symptoms differed in malnourished *versus* well-nourished groups: nausea ($p < 0.05$), hoarseness ($p < 0.01$), trouble swallowing ($p < 0.01$), and weight loss ($p < 0.001$). There were no statistically significant interaction effects of age with malnutrition, indicating that older and younger malnourished differed from well-nourished in a similar manner.

In regard to types of head and neck cancer, some of the younger but none of the older patients had tonsillar carcinoma ($p < 0.05$). Likewise, there were more cancers of the hypopharynx in malnourished than well-nourished patients ($p < 0.05$). Again, no interaction effects of age and nutritional status were found.

Nutritional Status

Table 3 shows the total PEMS scores for old and young malnourished and well-nourished patients. Although the proportion of patients who were malnourished did not differ by age (58% of old and 55% of young were malnourished), there was a significant interaction effect of age with nutritional status, in that the malnourished old had higher scores than any other group ($p < 0.05$). It can be seen that the old malnourished became more malnourished (about the same degree more as well-nourished patients) after surgery; however, the malnourished younger patients remained essentially at the same level of malnutrition.

Immune Status

Table 4 shows that lymphocyte responses to con A were lower in the old malnourished patients than in any other group after surgery. As expected, malnourished

TABLE 2. *Symptoms and Type of Cancer of Old and Young Malnourished and Well-nourished Patients*

Variables	Groups				*F* Ratios		
	Old		Young				
	Malnourished (N = 22)	Well-nourished (N = 16)	Malnourished (N = 23)	Well-nourished (N = 18)	Old *vs.* Young	Malnourished *vs.* Well-nourished	Age × Nutrition
Symptoms (%)							
Months since onset	2.8	3.0	5.7	4.5	5.4*	0.3	0.4
Pain	62	23	57	60	1.9	1.2	1.9
Trouble chewing	23	7	29	40	2.1	0.0	1.1
Nausea	13	0	21	0	0.8	4.1*	0.3
Hoarseness	50	15	71	30	3.4	7.5‡	0.6
Ulcer in mouth	38	15	35	40	0.9	0.3	0.8
Trouble swallowing	63	23	85	40	4.5*	9.7‡	0.2
Vomiting	0	0	14	0	1.8	1.5	1.3
Weight loss	62	0	86	50	16.6†	16.8†	1.3
Type of cancer (%)							
Tongue	10	22	12	23	0.1	1.3	0.0
Floor mouth	10	22	6	23	0.2	2.3	0.6
Palate	20	5	0	8	1.2	0.1	2.6
Tonsil	0	0	18	15	5.3*	0	0.1
Larynx	30	39	47	31	0.1	0.1	0.9
Hypopharynx	30	6	12	0	0.9	4.8*	0.6
Neck only	0	6	6	0	0.9	0.9	0.3

* $p < 0.05$.
† $p < 0.001$.
‡ $p < 0.01$.

and well-nourished patients differed significantly, with malnourished having lower immune function as reflected by lymphocyte responses to con A and by anergy. Doses yielding maximal responses were selected for analysis of lymphocyte function. Although response to delayed hypersensitivity skin testing was considered part of nutritional status measurement, it is shown here since it demonstrated the same *in vivo* cellular immune function pattern as that found for the *in vitro* lymphocyte response, with 60% of the old malnourished and 20% of the young malnourished being anergic (no response to all seven antigens).

Surgical Outcomes

Table 5 shows how the groups compared in regard to surgical outcomes. Days after surgery in the hospital were significantly more for malnourished than well-nourished patients ($p < 0.05$). Furthermore, more malnourished than well-nourished had greater degrees of postoperative complications ($p < 0.05$). However, significantly more of the old malnourished had more complications and significantly more of the old malnourished died within 1 year after surgery than any other group (both significant at the 0.05 levels). The relationship between nutritional status before surgery and surgical outcomes were examined. Greater degree of malnutrition, as reflected by the PEMS score, was correlated significantly with postoperative complications ($r = .42$, $p < 0.01$) and death within the year ($r = .59$, $p < 0.01$).

Preoperative Nutritional Support

In trying to account for the fact that the old malnourished became more malnourished after surgery while the younger malnourished did not, as well as for why the old

TABLE 3. *Nutritional Status before and after Surgery in Old and Young Malnourished and Well-nourished Patients*

Variables	Groups				*F* Ratios		
	Old		Young				
	Malnourished (N = 22)	Well-nourished (N = 16)	Malnourished (N = 23)	Well-nourished (N = 18)	Old *vs.* Young	Malnourished *vs.* Well-nourished	Age × Nutrition
Before surgery total PEMS	11.9	5.1	10.3	5.9	2.6	89.2*	3.8†
After surgery total PEMS	14.9	7.1	10.9	7.8	0.7	25.3*	5.9†

Note: Higher PEMS scores indicate more malnutrition.
* $p < 0.001$.
† $p < 0.05$.

TABLE 4. *Immune Function before and after Surgery in Old and Young Malnourished and Well-nourished Patients*

	Groups				*F* Ratios		
	Old		Young				
Variables	Malnourished (N = 22)	Well-nourished (N = 16)	Malnourished (N = 23)	Well-nourished (N = 18)	Old *vs.* Young	Malnourished *vs.* Well-nourished	Age × Nutrition
Before surgery							
Lymphocyte response							
to PHA	4.7	4.8	4.8	5.0	1.5	2.9	3.6
to con A	4.3	4.7	4.4	4.7	2.0	4.1*	1.2
Anergic (%)	60	0	20	0	5.1*	7.2†	4.8*
After surgery							
Lymphocyte response							
to PHA	4.5	4.7	4.7	5.0	3.3	2.4	1.0
to con A	4.1	4.6	4.3	4.6	2.6	4.4*	3.9*
Anergic (%)	60	0	20	10	4.6*	5.0*	4.3*

Note: Lymphocyte responses are given as counts per minute (cpm) in the stimulated minus control cultures with $\log_{10}$ transformation.

* $p < 0.05$.
† $p < 0.01$.

malnourished had the poorest outcomes of any group, the question of nutritional intervention before surgery was examined. None of the well-nourished in either age group received any type of nutritional support. Sixty per cent of the younger malnourished patients received either enteral or parenteral nutritional support before surgery. On the other hand, only 20% of the older malnourished patients received nutritional intervention before surgery.

Discussion

The major finding was that malnourished older patients had poorer surgical outcomes than any other group. The well-nourished elderly were similar in postoperative morbidity rates to younger patients. Since preoperative level of malnutrition was associated significantly with postoperative complications and death within 1 year, it seems likely that improving nutritional status before surgery, particularly in the elderly, might lead to decreased postoperative morbidity rates. This presents a dilemma for two reasons. One is that there is some suggestion here that the attitudes of staff about operating on the elderly and offering nutritional intervention may have played a role in their poorer surgical outcomes. If only older patients with lower clinical stages of cancer were selected for surgery then there is some systematic age bias in selection of patients. Further, if almost none of the malnourished old, but a sizeable proportion of the malnourished young, received nutritional intervention, and taking into account that the malnourished old were more malnourished than the malnourished young, then again there appears to be some age bias in the selection, unfortunately (in this case) for a clinical problem (malnutrition) that is remediable. What this suggests is that attitudes of the staff about treating the elderly may need to be explored further.

If chronologic age, rather than physiologic age, is the determinant of medical care, then the elderly may be given care that can result in premature morbidity and mortality rates.[12] There are additional suggestions of this

TABLE 5. *Surgical Outcomes in Old and Young Malnourished and Well-nourished Patients*

	Groups				*F* Ratios		
	Old		Young				
Variables	Malnourished (N = 22)	Well-nourished (N = 16)	Malnourished (N = 23)	Well-nourished (N = 18)	Old *vs.* Young	Malnourished *vs.* Well-nourished	Age × Nutrition
Days after surgery	40	18	39	13	0.4	4.2*	0.3
Complication score	7.6	4.0	4.4	2.5	3.7	5.4*	4.5*
Death (% 1 yr)	50	11	17	15	0.7	3.1	3.9*

Note: Complication score range is 0–12, with higher score being more severe.

* $p < 0.05$.

from other studies. One study[13] found that elderly patients with cancer received less curative treatments than younger patients with cancer even after taking stage of the disease into account. Likewise, a study[14] of 1680 women with breast cancer treated in 17 hospitals showed a linear trend for older patients to receive fewer services such as biopsies, number of lymph nodes examined, chemotherapy, and radiation therapy, even though stage of cancer and estrogen receptor status were not associated with age. Another recent study[15] controlled for comorbidity, functional status, and tumor stage, as well as for type and size of seven hospitals from which 374 cancer patients were selected. They found that even after controlling for all of these factors, age itself affected medical care in that physicians provided less than optimal care for older patients even with mild or no comorbid disease. Wetle[16] concluded that lack of data about treatment effectiveness and side effects for older patients made clinicians reluctant to use new treatments with the elderly or overly cautious by using less than optimal dosages. In turn, this leads to a self-fulfilling prophecy in which older patients treated for cancer *do not do well* because appropriate treatment was not provided. We have recently reported[17] that medical student attitudes about surgery in the elderly could be changed positively by a better understanding of the normal aging process and the need to evaluate each older person individually in regard to surgical risk based on his or her biologic and not chronologic age. Whether some emphasis in continuing medical education for staff or in the quality assurance review and feedback to staff would change attitudes about treating the elderly could be tested.

There is, however, another complicating factor that needs to be considered. Even if attitudes about operating on the elderly were improved and staff were motivated to offer nutritional intervention, the latter may be difficult to accomplish. Cost containment goals and diagnostic related groups (DRGs) have led to patients coming in only a day or two before elective surgery. We have found[18] that head and neck cancer patients admitted since institution of DRGs had significantly more malnutrition at the time of surgery and more postoperative complications than patients admitted before institution of DRGs. There is currently no system for reimbursement under DRGs for treating malnutrition. Thus, if preoperative nutritional support is needed, it may have to be offered in the home before hospital admission. The lack of time for intervention in the hospital applies equally to the young and old. However, there have been questions raised[19] about operations for the elderly and their necessity, with suggestions made that a third of the procedures may be unnecessary and that second opinions should be required for operations in the elderly. If such attitudes center only around the old, this can lead in a dangerous direction as a means of cost containment, because death, of course, can become the ultimate economy. The longer the elderly survive, the more costly their care.

At the same time that one might argue for equal treatment for all regardless of age, there are questions about the value of nutritional intervention in cancer. The role of cancer cachexia is not fully understood, particularly in how metabolism and immune function may be related. Malnutrition is known to suppress immune function. There is agreement that both malnutrition and immune function before surgery are associated with postoperative complications. However, studies have not clearly demonstrated that nutritional intervention in cancer patients can improve survival. There are questions as to whether total parenteral nutrition or overnutrition may in fact promote tumor growth.[20] The lack of effect of aggressive nutritional therapy on survival, however, should not be used to deny any cancer patient nutritional support during the course of illness. A better understanding, however, is needed about the effects of nutritional intervention, and most would agree that it should be used only for malnourished patients and perhaps then only in amounts adequate to supply needs and not tumor growth.

The comparison of old and young head and neck cancer patients showed several differences that require further study. Older patients seem to seek medical care earlier for symptoms than younger ones. The older patients also had fewer tonsillar cancers, which raises a question of whether this might be associated with the common practice of removing tonsils when the older men were children. Older patients never received preoperative chemotherapy, which also raises the question of possible age bias in clinical management. Why more pack/years of smoking was associated with being well-nourished, instead of being malnourished, cannot be answered, but the magnitude of the difference was 20 pack/years and occurred in both old and young groups between malnourished and well-nourished groups. Overall, there were perhaps more similarities than differences between old and young head and neck cancer patients. Mortality rates were very high in the malnourished old (50%) but lowest of any group in the well-nourished old (11%). In general, the findings suggest that more attention to the needs of the elderly in areas that could improve surgical outcome such as nutritional repletion might prove beneficial.

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Metabolic Intervention in Surgical Patients

An Assessment of the Effect of Somatostatin, Ranitidine, Naloxone, Diclophenac, Dipyridamole, or Salbutamol Infusion on Energy and Protein Kinetics in Surgical Patients Using Stable and Radioisotopes

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We have assessed the effect of a variety of forms of metabolic intervention on both energy and protein metabolism in 44 severely ill surgical patients. The patients were studied either in the basal state or while receiving total parenteral nutrition (TPN), and the metabolic effects were assessed using the primed-constant infusion of a combination of stable isotopes and radioisotopes. Somatostatin infusion, either in the basal state or in the TPN, did not change glucose kinetics, but there was a significant decrease in the rate of net protein catabolism (NPC). In the basal studies the rate of NPC decreased from 3.4 ± 0.7 g/kg/d to 2.9 ± 0.7 g/kg/d ($p < 0.002$), while in the TPN patients the corresponding values were 1.48 ± 0.61 g/kg/d and 1.10 ± 0.50 g/kg/d, respectively ($p < 0.005$). Histamine type 2 blockade with ranitidine did not significantly alter glucose kinetics, but in both the TPN patients and in the basal state ranitidine was associated with a significant decrease in the rate of NPC. In the basal state rate of NPC was 2.44 ± 0.53 g/kg/d and during ranitidine infusion the value was 2.08 ± 0.42 g/kg/d ($p < 0.04$). Naloxone infusion did not alter glucose kinetics, but there was a significant decrease in the rate of NPC from a basal value of 2.6 ± 0.6 g/kg/d to 2.3 ± 0.5 g/kg/d ($p < 0.04$). The infusion of the prostaglandin antagonists diclofenac or dipyridamole resulted in increases in the plasma insulin level, and as a result glucose turnover decreased in both groups. In the diclofenac group the rate of glucose turnover decreased from 14.4 ± 1.7 μmol/kg/min to 12.6 ± 1.3 μmol/kg/min ($p < 0.02$). Neither prostaglandin antagonist resulted in any significant change in the rate of NPC. Beta-adrenergic stimulation with salbutamol resulted in a significant increase in glucose turnover from 12.1 ± 1.1 μmol/kg/min to 13.4 ± 0.9 μmol/kg/min ($p < 0.02$), and the rates of appearance (Ra) of both alanine and free fatty acids (FFAs) also increased. Alanine Ra increased from 11.7 ± 2.5 μmol/kg/min to 12.8 ± 3.0 μmol/kg/min, and the corresponding values for FFA turnover were 7.6 ± 1.1 μmol/kg/min and 10.3 ± 2.1 μmol/kg/min ($p < 0.03$), respectively. Salbutamol infusion did not result in any significant change in the rate of NPC. We conclude from these studies the following: (1) The infusion of somatostatin, ranitidine, or naloxone results in a significant decrease in the rate of NPC in severely ill surgical patients both in the basal state and during TPN. (2) The aforementioned three agents do not influence glucose kinetics in any major way. (3) The infusion of prostaglandin antagonists does not result in any significant decrease in the rate of NPC, but insulin and cortisol levels change and glucose production decreases. (4) The infusion of the beta-agonist salbutamol results in the mobilization of both glucose and FFA, but there is no associated conservation of protein.

TOTAL PARENTERAL NUTRITION (TPN) has been widely used for a variety of reasons since its introduction approximately 25 years ago.[1] In a general sense TPN is a useful supportive modality especially in severely ill surgical patients who have a gut that is either blocked, inflamed, or patients who simply cannot cope.[2] Unfortunately, it has recently become apparent that although the use of TPN results in a decrease in the protein loss that accompanies critical surgical illness, only a minority of patients are rendered anabolic.[3–6] Patients with pure uncomplicated starvation are generally able to gain whole body protein with the use of TPN,[6,7] and upper gastrointestinal cancer patients can advance to a nutritional endpoint where they do not lose any more protein (the rate of whole body protein synthesis [WBPS] approximately equals the rate of whole body protein catabolism [WBPC]).[4,8] However, in severely stressed patients suffering from either trauma[9] or sepsis,[3,6] although the use of TPN results in a marked increase in WBPS, and as a result a major decrease in the rate of net protein loss, these patients remain in a state where net protein loss continues albeit at a slower rate than in the absence of TPN. Hill et al.[5,10] using *in*

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vivo neutron activation techniques have estimated that critically ill septic and/or trauma patients experience a loss of approximately 10% of their total body protein over a 2-week period despite the use of apparently state-of-the-art TPN.

The regulation of energy and protein metabolism in severely ill surgical patients has not been widely studied. Insulin is thought to have an anabolic role similar to the situation in normal humans, but there is a substantial body of data showing that in severely ill surgical patients insulin is less effective metabolically than in normal humans.[3,11,12] Glucagon cortisol and the catecholamines are known to be general promoters of the catabolic response to sepsis and/or trauma.[13,14] In particular both cortisol and glucagon are known to be promoters of both protein catabolism and gluconeogenesis from amino acids.[13,14] In addition, the beta-adrenergic nervous system is important in the promotion of fat mobilization,[15,16] while the alpha-adrenergic nervous system acts to inhibit lipolysis and promote proteolysis and glucose turnover.[15-17] The prostaglandin system, the endorphin system, and histamine are also thought to be involved in the regulation of the catabolic response, but the roles played by these agents are less clear.[13,14,18-22] Prostaglandin blockade with nonsteroidal anti-inflammatory agents such as ibuprofen or diclofenac has been shown to minimize the metabolic abnormalities that occur as a consequence of endotoxic shock,[21,22] but little work has been done to assess the effect of these type of agents in severely ill patients. Blocking the release of endorphins from the brain with the use of naloxone has been shown to improve survival in animals suffering from experimental shock[20]; however, few studies have been performed in severely ill patients. In addition, although much is known about the role of histamine as a mediator of the inflammatory response, its role in the mediation of the catabolic response to stress is less clear. Brackett et al.[18] have, however, recently shown that the use of H_1 and H_2 histamine receptor antagonists minimized the hemodynamic and metabolic abnormalities associated with endotoxemia in the conscious rat.

Because most critically ill surgical patients continue to have ongoing high rates of WBPC despite the use of TPN[3-6] and as a result of this an ongoing rate of protein loss, we have performed a series of studies to assess the effect of a variety of forms of metabolic intervention to conserve host tissue in severely ill surgical patients. These studies have been performed both in the basal state and also on patients receiving TPN. In particular, we have assessed the metabolic and hormonal changes associated with the following perturbations: somatostatin infusion to decrease insulin, growth hormone (HGH), and glucagon availability[23]; histamine type 2 (H_2) blockade using the infusion of ranitidine[18,24]; naloxone infusion to decrease endorphin availability[19]; and two forms of prostaglandin blockade using either diclofenac or dipyridamole.[20-22,24,25] In addition, in view of the fact that fat is probably a preferred fuel in severely stressed patients,[25-29] and because fat mobilization is a beta-adrenergic effect,[15,16] we have also assessed the metabolic and hormonal response to beta-adrenergic stimulation by infusing the beta-agonist salbutamol.

Materials and Methods

Studies were performed in 44 severely ill surgical patients. Most of the patients were suffering from either pancreatitis, some form of cancer, sepsis, or trauma, and the clinical details of the group are summarized in Table 1. In all cases the patients were at least 12 hours postabsorptive at the time of study.

The study was approved by the institutional board at Auckland Hospital, and the use of radioisotopes was approved by the National Radiation Laboratory (New Zealand).

Experimental Protocol

All experiments involved the infusion of isotopes and the collection of blood samples.

The experiments each consisted of two periods (periods 1 and 2). At the start of period 1 a primed-constant infusion of isotopes was started and maintained for the duration of the study. Period 1 lasted for 180 minutes and blood samples were taken over the last 60 minutes. During the 120 minutes of period 2, in both the patients and volunteers the isotopic infusion was continued, and the system was perturbated using one of seven types of metabolic intervention. Blood samples were taken again during period 2. In addition, ten infusions were performed where there was no perturbation in period (isotopes alone were infused throughout).

Types of Metabolic Intervention Employed

In period 2 of each study there was either no perturbation (control protocol) or one of seven perturbations was induced. These were: (1) the infusion of somatostatin (0.15 μg/kg/min) in order to decrease glucagon, HGH, and insulin availability; (2) the infusion of somatostatin and insulin in order to selectively reduce the plasma levels of HGH and glucagon while maintaining the plasma insulin level approximately constant. Here the somatostatin infusion rate was as for (1), and, in addition, insulin was infused at approximately 0.05 mIU/kg/min; (3) the infusion of the histamine type 2 blocking agent ranitidine at a rate of 6 μg/kg/min in order to induce a state of partial histamine blockade; (4) the infusion of naloxone at a rate of 0.1 μg/kg/min in order to decrease endorphin availability; (5) the infusion of the beta-adrenergic agonist salbutamol at a rate of

TABLE 1. *Clinical Details of Patients*

Patient No.	Age	Sex	Diagnosis	Protocol
1	21	F	Trauma femur, arterial	SOM
2	81	M	Mesenteric infarction	SOM-INS
3	65	F	Trauma chest, arterial	SOM-INS
4	49	M	Cancer colon	SOM, SOM-INS
5	47	M	Cancer esophagus	SOM, SOM-INS
6	77	M	Cancer colon	SOM-INS
7	81	F	Cancer stomach	SOM-INS
8	75	M	Sepsis abdomen	RAN, SOM-TPN,
9	21	F	Trauma abdomen, limbs	SOM-TPN, RAN-TPN
10	68	M	Cancer pharynx	SOM-TPN, RAN-TPN
11	87	F	Sepsis mediastinum	SOM-TPN, RAN-TPN
12	46	M	Cancer pancreas	SOM-TPN
13	18	F	Trauma abdomen, limbs	SOM-TPN, RAN-TPN
14	23	M	Trauma abdomen, chest	SOM-TPN
15	56	M	Trauma abdomen	SAL
16	53	F	Trauma abdomen	SAL
17	57	M	Trauma abdomen	SAL
18	45	M	Trauma abdomen	SAL
19	46	M	Trauma abdomen	SAL
20	30	M	Trauma abdomen	SAL
21	65	M	Cancer duodenum	SAL
22	50	M	Pancreatitis	NARC, VOLT
23	22	M	Trauma abdomen	NARC
24	25	M	Trauma abdomen	NARC
25	30	M	Trauma abdomen	NARC
26	44	M	Peptic Ulcer	VOLT
27	18	M	Trauma abdomen	VOLT
28	23	M	Trauma abdomen	VOLT
29	24	M	Trauma abdomen	VOLT
30	58	M	Pancreatitis	PERS
31	77	M	Pancreatitis	PERS
32	24	M	Trauma abdomen	PERS
33	49	M	Trauma abdomen	PERS
34	61	F	Cancer colon	RAN
35	83	F	Cancer colon	RAN
36	67	M	Cancer pancreas	RAN
37	63	F	Cancer bile duct	RAN
38	53	F	Short gut syndrome	RAN
39	63	M	Cancer neck	RAN
40	23	M	Trauma head, chest	RAN
41	75	M	Sepsis abdominal	RAN
42	75	M	Cancer stomach	RAN
43	57	M	Cancer pancreas	RAN

SOM = somatostatin infusion.
SOM-INS = somatostatin-insulin infusion.
RAN = ranitidine infusion.
SAL = salbutamol infusion.
NARC = naloxone infusion.
PERS = dipyridamole infusion.
VOLT = diclofenac infusion.
TPN = patient receiving TPN during study.

0.12 μg/kg/min in order to promote beta-adrenergic activity; (6) the infusion of either diclofenac (0.01 mg/kg/min) or dipyridamole (1.2 μg/kg/min) in order to inhibit prostaglandin synthesis.

The aforementioned types of metabolic intervention were performed in patients in the basal state (at least 12 hours postabsorbtive). Furthermore, the effect of either somatostatin infusion or ranitidine infusion was assessed in patients established on TPN. The patients were studied when they had been on TPN on average for 1 week, protein was provided at 2 g/kg/d, and calories were provided at a rate of 40 kcal/kg/d with 50% of calories being provided as fat and 50% as glucose. The details of the various perturbations performed in each patient are shown in Table 1.

Isotopic Infusions and Calculations

A combination of stable and radioisotopes were used. Glucose kinetics were determined using the primed-constant infusion of 6-^{3}H glucose as we have described before,[30] and urea kinetics were determined using the primed-constant infusion of ^{14}C urea as we have described previously.[30,31] Alanine rate of appearance was determined using the primed-constant infusion of 3-^{13}C alanine as described elsewhere,[32] and FFA kinetics were quantitated using 1-^{13}C-palmitic acid as described elsewhere.[33]

The primed-constant infusion of either 15N lysine or 1-^{13}C leucine was used to determine amino acid turnover,[34] and from these data rates of WBPS and WBPC

TABLE 2. *Plasma Hormone Levels and the Effect of Metabolic Manipulation*

		BASAL:SOM	BASAL:SOM-INS	TPN:SOM	RAN, NARK, SAL, TPN:RAN	VOLT	PERS
Insulin (mIU/L)	1	17 ± 4	14 ± 9	75 ± 15	NS	20 ± 7	50 ± 9
	11	2 ± 2*	22 ± 13	30 ± 18*	—	24 ± 6*	71 ± 28†
HGH (pg/L)	1	1.9 ± 0.3	—	—	—	—	—
	11	1.0 ± 0.1*	—	—	—	—	—
Glucagon (ng/L)	1	166 ± 33	166 ± 33	—	—	—	—
	11	121 ± 18*	105 ± 15†	—	—	—	—
Cortisol	1	438 ± 67	—	511 ± 691	—	—	319 ± 59
	11	370 ± 67	—	551 ± 69	NS	—	237 ± 37

* Significantly different from period 1 value ($p < 0.05$).
† Significantly different from period 1 value ($p < 0.08$).
NS = no significant difference between period 1 and period 2 values.
SOM = somatostatin infusion during period 2.
SOM-INS = somatostatin and insulin infused during period 2.
RAN = ranitidine infusion during period 2.
NARK = naloxone infusion during period 2.
SAL = salbutamol infusion during period 2.
VOLT = diclofenac infusion during period 2.
PERS = dipyridamole infusion during period 2.

were determined as described previously.[35] Rates of NPC were calculated from the urea rate of appearance data as described previously.[30,32]

Rate of appearance calculations were performed using the Steele equation[36] in the case of radioisotopes, and for 15N and ^{13}C labeled tracers the Steele equation was modified appropriately.[30,31,33,34]

Statistical Analyses

Because there were no significant changes in either kinetic or hormonal levels between period 1 and 2 in the control studies, the data obtained in period 2 of each study were compared with the corresponding period 1 data using a paired t-test. In addition, the data obtained in the various groups were compared using ANOVA.

Analysis of Samples

Blood samples were immediately chilled and later centrifuged to separate the plasma.

Plasma glucose specific activity and urea specific activity were determined as described elsewhere.[30] We have previously described the methods by which plasma 15N lysine and ^{13}C leucine enrichment were determined,[3,4,34] as well as the method by which the enrichment of ^{13}C palmitate was determined.[33]

Serum levels of insulin, growth hormone, and cortisol were determined by radioimmunoassay.[37-39]

Results

Hormones

Somatastatin infusion resulted in a significant decrease in the plasma levels of insulin, glucagon, and HGH. The plasma level of cortisol did not change in any of the protocols in which somatostatin was infused (Table 2).

Ranitidine infusion did not significantly change the plasma levels of cortisol or insulin in the basal state or during TPN (Table 2).

Neither the infusion of naloxone nor salbutamol resulted in any significant change in the plasma levels of insulin or cortisol. However, the infusion of both diclofenac and dipyridamole resulted in an increase in the plasma insulin level ($p < 0.05$ for diclofenac, and $p < 0.08$ for dipyridamole). In addition, dipyridamole infusion resulted in a significant decrease in the plasma cortisol level ($p < 0.03$) (Table 2).

Somatostatin Infusion

When somatostatin alone was infused there was no significant change in either the plasma glucose concentration or in the rate of glucose turnover. As a consequence, the rate of glucose clearance also did not change. The basal rate of glucose turnover in these studies was 19.0 ± 3.6 µmol/kg/min, and during somatostatin infusion the value was 20.1 ± 3.2 µmol/kg/min. When somatostatin was infused in the TPN patients the effect was similar; there was no significant change in the plasma glucose level or in the rate of glucose turnover or glucose clearance (Fig. 1).

When both somatostatin and insulin were infused there was a selective reduction in the plasma levels of glucagon and HGH while the plasma insulin level did not change significantly. In this setting the plasma glucose level decreased from 6.9 ± 0.7 µmol/mL to 4.8 µmol/mL ($p < 0.05$), and the rate of glucose turnover decreased from 17.6 + 2.2 µmol/kg/min to 11.1 ± 2.5 µmol/kg/min ($p < 0.01$). The rate of glucose clearance also decreased from 2.7 ± 0.3 mL/kg/min to 2.3 ± 0.3 mL/kg/min ($p < 0.04$) (Fig. 1).

Somatostatin infusion resulted in a decrease in urea turnover in each of the three protocols. When somatostatin was infused alone, the rate of urea turnover decreased from 13.4 ± 2.9 µmol/kg/min to 11.8 ± 2.0 µmol/kg/min ($p < 0.002$). The infusion of somatostatin and insulin resulted in a similar magnitude of change ($p < 0.007$); the basal value was 11.3 ± 2.5 µmol/kg/min

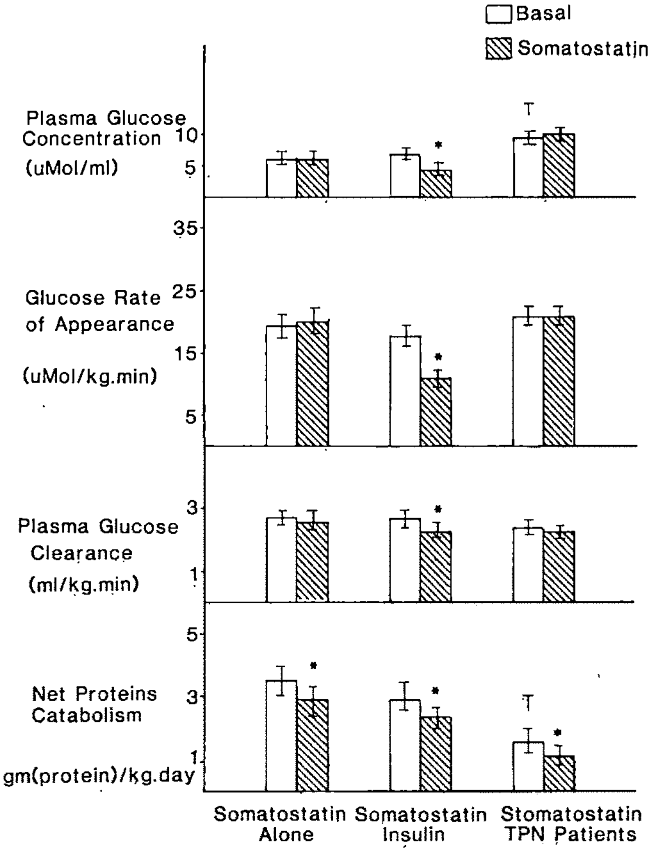

FIG. 1. Glucose kinetics and NPC in patients and the effect of somatostatin infusion. * Significantly different from preceding value ($p < 0.05$ or better). T, significantly different from corresponding basal value ($p < 0.05$ or better).

and the period 2 value was 9.5 ± 2.1 μmol/kg/min. In the TPN patients the basal rate of urea turnover was 14.0 ± 2.8 μmol/kg/min and during somatostatin infusion this decreased to 12.5 ± 2.5 μmol/kg/min ($p < 0.005$).

The period 1 and period 2 values for NPC calculated from the urea kinetic data were as follows: somatostatin infusion alone, 3.4 ± 0.7 and 2.9 ± 0.7 g/kg/d ($p < 0.002$); somatostatin/insulin infusion, 2.8 ± 0.7 and 2.4 ± 0.5 g/kg/d ($p < 0.007$); somatostatin/TPN, 1.47 ± 0.61 and 1.10 ± 0.50 g/kg/min ($p < 0.05$). The basal value for the rate of NPC in the TPN patients (1.47 ± 0.62 g/kg/day) was significantly lower ($p < 0.01$) than the overall value for NPC in the basal state (3.1 ± 0.8 g/kg/d).

The basal rate of WBPC in the TPN patients overall was 7.3 ± 1.5 g/kg/d (NS, less than the basal value). In the TPN patients in whom the effect of somatostatin infusion was assessed, the basal value for WBPC was 8.2 ± 2.1 g (protein)/kg/d, and during somatostatin infusion this decreased to 6.6 ± 1.6 g/kg/d ($p < 0.03$) (Fig. 2). Somatostatin infusion did not significantly alter the rate of WBPS in the TPN patients.

Ranitidine Infusion

Ranitidine infusion did not alter either the plasma glucose level or the rate of glucose turnover when infused either in the basal state or during TPN. In the basal state the rate of glucose turnover was 17.3 ± 2.8 μmol/kg/min, and during ranitidine infusion the corresponding value was 17.2 ± 3.0 μmol/kg/min. In the TPN patients the basal rate of glucose turnover was 18.6 ± 1.7 μmol/kg/min, and during ranitidine infusion the value was 17.1 ± 1.5 μmol/kg/min (Fig. 1).

Ranitidine infusion resulted in a suppression of the rate of NPC. The basal rate of NPC for the ranitidine group as a whole was 2.44 ± 0.53 g/kg/d, and during ranitidine infusion this decreased to 2.08 + 0.42 g/kg/d ($p < 0.03$).

In the TPN patients ranitidine infusion was associated with a decrease in urea turnover from 11.9 ± 1.6 μmol/kg/min to 10.5 μmol/kg/min. In these patients the glucose infusion rate was 3.3 ± 0.3 mg/kg/min, the lipid infusion rate (20% lipid emulsion) was 0.007 ± 0.0003 mL/kg/min, and the protein infusion rate was 1.9 ± 0.3 g/kg/d. Under these circumstances this decrease in urea turnover represented a significant decrease in the rate of NPC from 1.10 ± 0.33 g/kg/d to 0.88 ± 0.25 g/kg/d ($p < 0.05$) (Fig. 2).

The basal rate of WBPC in the ranitidine infusion group was 3.9 + 0.8 g/kg/d, and during ranitidine infusion this decreased to 3.2 + 0.5 g/kg/d ($p < 0.03$). The basal rate of WBPS calculated from the WBPC and NPC data did not change significantly following ranitidine infusion (Fig. 3).

The rate of WBPC in the TPN patients prior to ranitidine infusion was 6.5 + 1.0 g/kg/d, and during ranitidine infusion the value was 5.5 + 0.8 g/kg/d ($p < 0.02$). The rate of WBPS did not change significantly during ranitidine infusion in the TPN patients (Fig. 3).

Salbutamol Infusion

Salbutamol infusion resulted in a significant increase in both the plasma glucose concentration and in the rate of glucose turnover. The basal value for glucose concentration was 7.2 ± 0.6 μmol/mL, and in period 2 the value was 7.9 + 0.6 μmol/mL. The basal rate of glucose turnover was 12.1 ± 1.1 μmol/kg/min, and during salbutamol infusion this increased to 13.4 ± 0.9 μmol/kg/min ($p < 0.02$). This increase in glucose turnover was associated with an increase in the rate of alanine appearance into the plasma; the basal rate of alanine appearance was 11.7 ± 2.5 μmol/kg/min and during salbutamol infusion this increased to 12.8 ± 3.0 μmol/kg/min. The rate of FFA appearance also increased during salbutamol infusion; the basal value was 7.6 ± 1.1 μmol/kg/min and during salbutamol infusion this increased to 10.3 ± 2.1 μmol/kg/min ($p < 0.04$).

The basal rate of urea turnover in the salbutamol

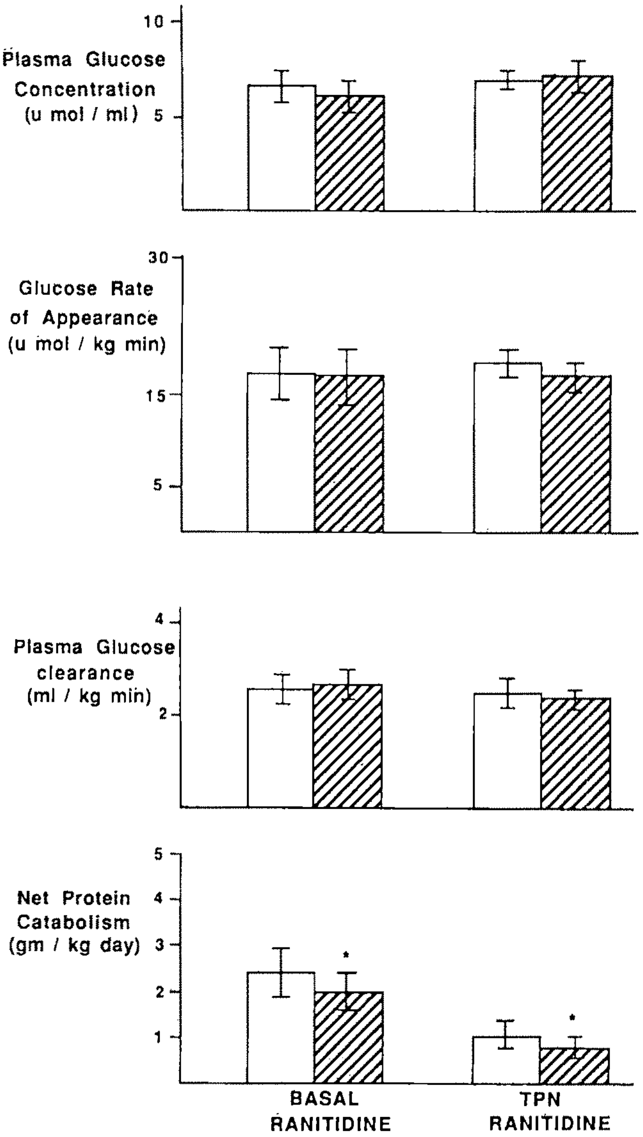

FIG. 2. Glucose kinetics and NPC in patients and the effect of ranitidine infusion. * Significant difference compared with preceding value ($p < 0.05$ or better).

group was 7.7 ± 1.8 μmol/kg/min, and during salbutamol infusion the value was 7.3 ± 1.5 μmol/kg/min (NS) (Fig. 4).

Naloxone Infusion

Naloxone infusion was not associated with any significant change in either the rate of glucose turnover or glucose clearance. The basal rate of glucose turnover was 18.5 ± 2.0 μmol/kg/min and during naloxone infusion the corresponding value was 17.5 ± 3.0 μmol/kg/min. The basal value for plasma glucose concentration was 7.9 ± 0.6 μmol/mL, and in period 2 the value was 7.8 ± 0.4 μmol/mL.

The basal rate of urea turnover was 10.3 ± 2.4 μmol/kg/min, and during naloxone infusion this decreased to 9.3 ± 2.1 μmol/kg/min ($p < 0.04$). From these values

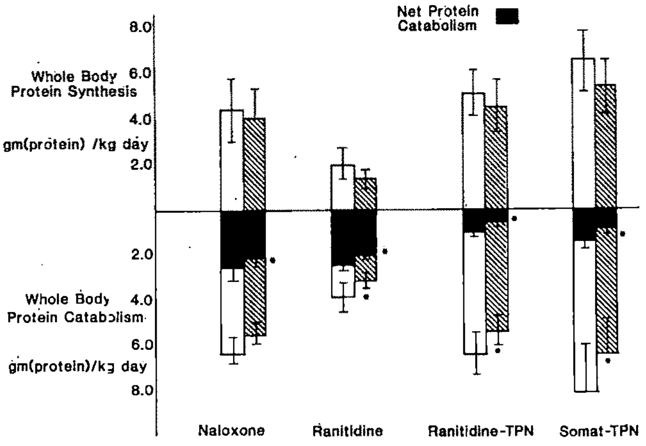

FIG. 3. Whole body protein kinetics in patients and the response following various types of metabolic intervention. Values are given as mean ± SEM. * Significantly different from preceding value ($p < 0.05$).

the basal rate of NPC was 2.60 ± 0.60 g/kg/d, and during naloxone infusion this decreased significantly to 2.34 ± 0.53 g/kg/d ($p < 0.04$). The basal rate of WBPC was 6.3 ± 0.9 g/kg/d, and during naloxone infusion this decreased to 5.7 ± 0.9 g/kg/d (Figs. 3 and 4).

Diclofenac Infusion

The basal rate of glucose turnover in these patients was 14.4 ± 1.7 μmol/kg/min, and during diclofenac

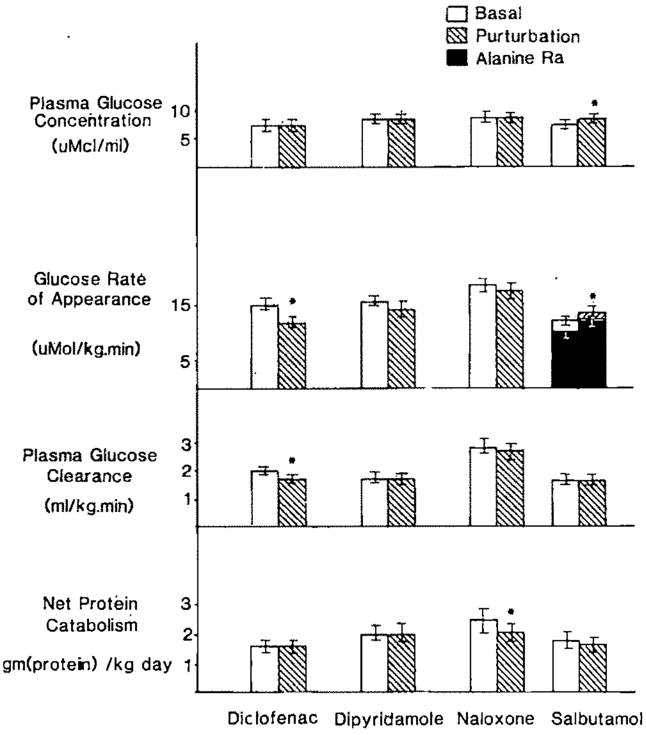

FIG. 4. Glucose kinetics and NPC in surgical patients and the effect of pharmacologic manipulation. * Significantly different from preceding value ($p < 0.05$ or better).

(VOLT) infusion this decreased significantly to 12.6 ± 1.3 μmol/kg/min ($p < 0.02$). The basal rate of plasma glucose clearance was 2.0 ± 0.1 mL/kg/min, and during VOLT infusion this decreased to 1.8 ± 0.1 mL/kg/min ($p < 0.05$). As a result, the plasma glucose concentration did not change significantly. The period 1 and period 2 values were 7.2 ± 0.8 μmol/mL and 7.2 ± 0.6 μmol/mL, respectively.

The basal rate of urea turnover was 6.4 ± 1.2 μmol/kg/min, and during VOLT infusion the value was 6.2 ± 1.1 μmol/kg/min (NS) (Fig. 4).

Dipyridamole Infusion

Dipyridamole (PERS) infusion did not result in any change in either the plasma glucose concentration or in the rate of glucose appearance. The basal values for plasma glucose concentration, glucose rate of appearance, and plasma glucose clearance were 8.1 ± 1.1 μmol/mL, 15.5 ± 1.1 μmol/kg/min, and 1.8 ± 0.2 mL/kg/min, respectively.

VOLT infusion did not significantly alter the rate of FFA appearance or the rate of urea appearance. The basal rate of FFA appearance was 8.1 ± 3.6 μmol/kg/min, and during VOLT infusion the value was 7.9 ± 2.0 μmol/kg/min. The basal rate of urea turnover was 8.2 ± 1.8 μmol/kg/min, and during VOLT infusion the value was 8.4 ± 2.0 μmol/kg/min (NS) (Fig. 4).

Discussion

In a general sense, our study highlights the complexity of the processes involved in the regulation of metabolism in severely ill surgical patients; despite the fact that our study has outlined the importance of a number of regulatory mechanisms, we have probably only scratched the surface, and a host of other regulatory processes are also of importance.

The somatostatin studies allowed us to differentiate between the effects of a variety of hormones. The infusion of somatostatin alone resulted in a significant suppression in the plasma levels of insulin, glucagon, and HGH, and this was associated with a significant decrease in the rate of net protein loss both in the basal state and in the patients who were established on TPN. The decrease in insulin availability would not have promoted this decrease in protein loss since insulin is known to be a potent anabolic hormone.[13,14] A decrease in HGH availability probably would also not have promoted this decrease in NPC since Mason and Wilmore[40] have recently shown that the infusion of HGH is associated with an improvement in protein balance, and cortisol could not have been responsible since the plasma cortisol level did not change significantly following somatastin infusion. We have previously shown that glucagon is important in the mediation of the metabolic response to stress in septic animals,[16] and in the present study the decrease in NPC following somatostatin infusion was associated with a significant decrease in the plasma glucagon concentration. Our data are also consistent with a number of animal studies (*e.g.*, Salter et al.[41]) that have shown that glucagon promotes protein catabolism *in vitro*. The failure of somatostatin infusion alone to induce any change in glucose kinetics is probably explained by the changes in the insulin:glucagon (I:G) ratio that occurred following somatostatin infusion. In the basal state the I:G ratio was 0.1 and when somatostatin was infused this decreased to 0.02. This response would have favored an increase in glucose turnover,[41] but, on the other hand, this effect would have been opposed by the decrease in the HGH level since HGH is known to promote glucose production.[40] When somatostatin was infused and a state of hyperinsulinemia maintained, in contrast to what was seen during somatostatin infusion alone, the I:G ratio increased from 0.08 to 0.2, and this was associated with a significant decrease in glucose turnover and, consequently, in glucose clearance. The role of insulin infusion in the regulation of net protein loss appeared to be relatively minor in the patients we studied since the degree of protein sparing that followed somatostatin infusion was of similar magnitude irrespective of whether or not insulin was also infused.

The effect of ranitidine infusion was similar to that of somatostatin: no change in glucose kinetics and a significant decrease in the rate of protein loss both in the basal state and during TPN. Again, as with somatostatin infusion the protein sparing effect of ranitidine infusion was independent of both insulin and cortisol, and the degree of effect was similar in the three groups assessed. It is not possible to determine from our study whether the effect of the ranitidine infusion on protein loss was via a H_2 type blockade or via another mechanism. The dose of ranitidine we used is known to be effective in inducing H_2 blockade of the parietal cell mass in severely ill surgical patients,[42] and histamine blocking agents are known to minimize the metabolic effects of experimental septic shock in animals,[18] an effect thought to be mediated via the histamine receptor system. On this basis, it is likely that the effect of ranitidine to reduce protein loss in these patients was via the blockade of histamine type 2 receptors, although specific experiments would be required to prove this.

The fact that neither of the prostaglandin inhibitors resulted in any significant decrease in protein loss is in contrast with what we predicted would happen from available animal data. *In vitro* studies have shown that in general terms the prostaglandin system is involved in the promotion of muscle catabolism, and, on this basis, it appeared likely that the infusion of agents known to be prostaglandin antagonists would result in a decrease in protein loss in the patients we studied. It is possible that the agents we employed did not antagonize the specific

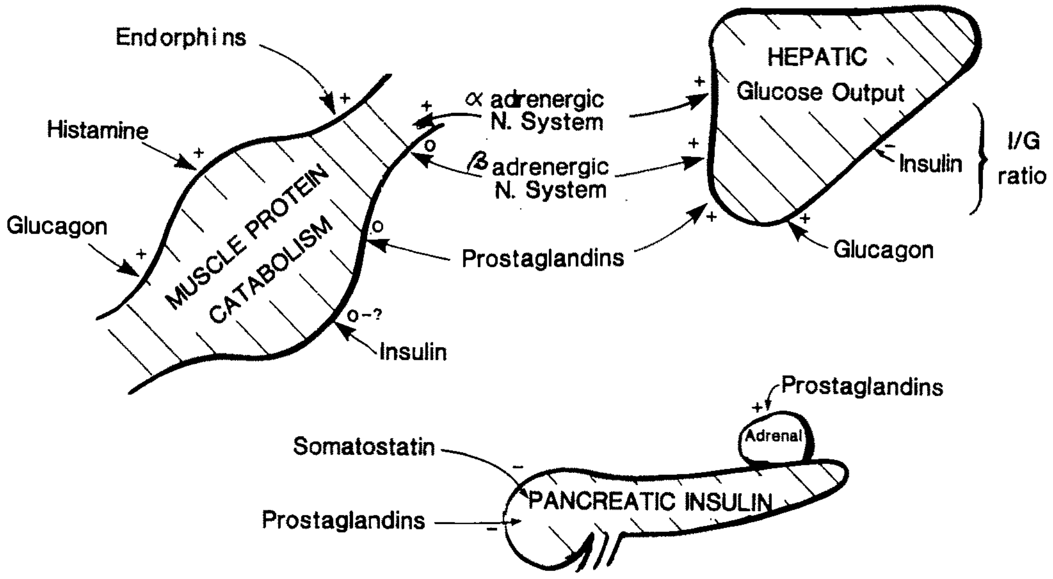

FIG. 5. An integrated assessment of the roles of glucagon, insulin, endorphins, the adrenergic nervous system, and prostaglandins in the regulation of muscle and liver metabolism. + = stimulatory effect; − = inhibitory effect; 0–? = no effect or possible effect; I/G ratio = insulin/glucagon ratio; N. System = nervous system.

prostaglandins responsible for the promotion of muscle catabolism, or, alternatively, that there was an inhibition of the activity of both the inhibitory and stimulatory prostaglandins (with respect to protein breakdown). Our findings agree with those of others who were also unable to demonstrate a protein sparing effect of prostaglandin blockade *in vivo.*[43] The prostaglandin blocking agents did, however, have a number of hormonal effects. The infusion of either agent resulted in an increase in the plasma insulin level ($p < 0.05$ in the case of diclofenac), and in both cases this change in the plasma insulin level was associated with a decrease in glucose turnover ($p < 0.05$ in the diclofenac group). Despite these increases in the plasma insulin level and in the dipyridamole group and associated significant decrease in the plasma cortisol level, there was no effect on protein sparing. This was surprising since both of these hormonal responses would have been expected to favor protein conservation.[13,14]

Naloxone has been shown to improve survival in animals subjected to experimental septic shock[19] via an inhibition of endorphin availability. Our study failed to show any effect of naloxone on glucose turnover, or on the levels of insulin, cortisol, or FFA. However, the infusion of naloxone was associated with a small but statistically significant decrease in protein loss. This finding is consistent with the animal data of Holaday and Faden[19] who found that naloxone minimized the metabolic changes induced by endotoxemia. It is likely that the same mechanism was involved in the patients we studied, but this is not conclusively proved in our study and specific experiments would be required to elucidate this.

We have previously shown that fat is a preferred energy source both in severely ill animals and in severely ill surgical patients.[26–28] In addition, the promotion of lipolysis is a beta-adrenergic effect[15] that is inhibited by beta-adrenergic blockade and promoted by beta-adrenergic stimulation.[15] On this basis, we thought it was likely that the promotion of the availability of a preferred energy substrate (FFA) would possibly exert a protein sparing effect. Our study showed that beta stimulation with salbutamol resulted in an increase in FFA turnover, but there was also an increase in alanine appearance in the plasma, presumably arising from muscle catabolism.[44] This latter effect would have been expected to have been associated with an increase in catabolism and, therefore, in urea rate of appearance, but this was not seen. We have previously shown that changes in alanine rate of appearance and changes in urea turnover do not always go hand in hand (*e.g.,* during glucose infusion[33]), and this present observation appears to be another such example. Thus, although the promotion of lipolysis would probably be a desirable effect in these patients, beta-adrenergic stimulation was not associated with a conservation of protein; rather the release of alanine (presumably from muscle) actually increased.

By integrating the data from the various protocols in this series of studies it is possible to develop a model of the regulation of energy and protein metabolism in severely ill patients. This is summarized in Figure 5.

In summary, our study shows the following: (1) Somatostatin infusion and ranitidine infusion both result in a small but significant decrease in the rate of protein loss in severely ill surgical patients, both in the basal state and during TPN. The primary mechanism is via a decrease in WBPC, and in the TPN patients this is a particularly important response since we have previously shown that the use of TPN alone does not result in a suppression of the elevated rate of WBPC usually seen in severely ill surgical patients,[3,4] the protein sparing effect being purely due to a promotion of WBPS. (2) The infusion of the prostaglandin blocking agents dipyridamole and diclofenac induced changes in serum hormonal levels and changes in glucose kinetics, but neither agent resulted in any conservation of protein. (3) Beta-adrenergic stimulation with salbutamol induces an increase in FFA availability, but there is no decrease in the rate of net protein loss following the infusion of this agent, and the rate of appearance of alanine into the plasma actually increases. (4) Naloxone infusion does not result in any significant change in either plasma insulin or cortisol levels or in glucose kinetics, but there is a small but significant decrease in the rate of net protein loss. As is the case with somatostatin and ranitidine, this effect appears to be via a decrease in WBPC. (5) Despite the fact that the magnitude of the changes in protein loss following the use of these agents is small with the dosages used, the use of combined agents or higher doses of individual agents might conceivably produce a more pronounced effect.

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Energy and Protein Metabolism in Sarcoma Patients

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We have performed a series of isotopic infusions both in normal volunteers (N = 16) and in sarcoma patients (N = 7). Using the primed-constant infusion of stable or radioisotopes we have determined the rates of glucose turnover, glucose oxidation, glucose recycling, and net protein catabolism (NPC). In addition, we have measured VO_2 and VCO_2. The values for VCO_2 and VO_2 were higher in the patients than in the volunteers (mean VO_2 values in volunteers and patients: 107 ± 13 and 158 ± 13 μmol/kg/min, respectively). The basal rate of glucose appearance in the sarcoma patients was twice the value seen in the volunteers (28.3 ± 3.5 *vs.* 13.9 ± 0.3 μmol/kg/min). Glucose infusion in the volunteers resulted in virtually total suppression of endogenous glucose production, while in the patients glucose infusion induced only a 30% suppression of endogenous glucose production ($p < 0.01$). The rate of glucose clearance in the patients was approximately twice the value seen in the volunteers [5.4 ± 1.0 *vs.* 2.7 ± 0.1 mL/kg/min ($p < 0.01$)]. The per cent of glucose uptake oxidized in the patients was significantly less than in the volunteers [22% *vs.* 36% ($p < 0.05$)], and the per cent of glucose uptake that was recycled was significantly higher in the patients [55% *vs.* 10% ($p < 0.01$)]. In addition, the basal rate of net protein loss was increased twofold in the patients [3.2 ± 0.5 *vs.* 1.4 ± 0.4 g (protein)/kg/d ($p < 0.01$)], and in contrast to the situation in the volunteers there was no suppression in the rate of net protein loss when the patients were infused with glucose. The basal insulin concentration and the insulin response to glucose infusion in the patients were similar to that of the volunteers, but the plasma cortisol level was similar in volunteers and in the patients ($p < 0.05$). We conclude from these studies the following: (1) Sarcoma patients have significantly elevated rates of glucose production and glucose clearance, but they have an impaired capacity to directly oxidize either endogenous or infused glucose, coupled with an increased rate of glucose recycling. (2) Sarcoma patients have an elevated metabolic rate and are catabolic. In addition, in contrast with normal volunteers, glucose infusion does not result in a suppression of protein loss.

ENERGY AND PROTEIN METABOLISM in cancer patients has been widely studied by a number of investigators.[1–4] In a general sense, it is clear that there is a metabolic reaction of the host in response to the presence of a malignant tumour, especially if there is advanced disease.[2] However, it is difficult to formulate a clear picture regarding the specific details of the individual metabolic changes that occur in response to particular types of cancer.

A number of studies addressing the metabolic response to tumour bearing have not accounted for the possible variations in metabolic response that might exist between patients with cancers of different histologic type.[5] A number of investigators have shown that there are substantial metabolic differences depending on the anatomic site and histologic type of the cancer. Buzby et al.,[4] for example, have shown that pancreatic cancer patients have low metabolic rates whereas patients with lung cancer or malignant lymphoma tend to have high metabolic rates. We have previously shown that patients with lower gastrointestinal (GI) cancer are metabolically similar to normal volunteers, while patients with upper GI cancer have elevated rates of lipolysis, glucose turnover, and an increased reliance on glucose as an energy substrate.[5,6] In addition, we have demonstrated that patients with advanced head and neck cancer are also metabolically abnormal, having accelerated rates of glucose turnover, glucose recycling, and a loss of the protein-sparing response to starvation.[7]

In a general sense, based on available data in the literature (mainly from animals), it appears likely that sar-

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TABLE 1. *Clinical Detals of Patients*

Patient No.	Age	Sex	Diagnosis and Stage of Disease	% Weight Loss†
1	21	M	Osteogenic sarcoma femur, lung METS*	<5
2	67	M	Retroperitoneal MFH, no METS	8
3	76	M	Liposarcoma thigh, no METS	0
4	17	M	Osteogenic sarcoma thigh, lung METS*	<5
5	80	F	Retroperitoneal liposarcoma, no METS	20
6	71	F	Liposarcoma forearm, no METS	0
7	80	F	Anaplastic neuroendocrine sarcoma scalp, lung METS	10

* Primary lesion had been resected previously.

† % weight loss was estimated on the basis of previous well weight.

METS = metastatic disease present.

MFH = malignant fibrous histiocytoma.

Patient nos. 2, 3, and 5 had bulky disease (tumour bulk >0.5 kg) Patient nos. 1 and 4 had previously had bulky primary disease, but at the time of study the only known disease was multiple bilateral lung metastases in both cases. Patient no. 6 had a small primary lesion weighing <150 g. Patient no. 7 had 150 g of primary tumor, 150 g of tumor in neck nodes, and bilateral pulmonary metastases.

coma patients probably display a number of metabolic abnormalities, and they may also differ from GI cancer patients or head and neck cancer patients. Brennan et al.[8] have shown that sarcoma-bearing animals have high metabolic rates, high rates of glucose turnover,[9] high rates of glucose recycling,[10] and enhanced rates of both protein synthesis and degradation.[11] In addition, Norton et al.[12] have shown that sarcoma patients are glucose intolerant.

In view of the fact that (1) sarcoma patients do not infrequently require nutritional support as an adjunct to what is often aggressive anticancer therapy and (2) very few metabolic studies have been performed in sarcoma patients, we have performed a series of studies to address a number of aspects of energy and protein metabolism in a group of sarcoma patients. In particular, we have used isotopic tracer methodology to measure rates of glucose turnover, glucose oxidation, and net protein catabolism (NPC) both in the basal state and during glucose infusion. In addition, we have estimated plasma insulin and cortisol values, and have determined rates of oxygen consumption and CO_2 production. The responses seen in the sarcoma patients have been compared with similar data obtained in a group of normal volunteers.

Materials and Methods

Studies were performed in 16 normal volunteers, and in seven sarcoma patients. In all instances the patients (all volunteers) were at least 12 hours postabsorptive at the time of study.

The study was approved by the institutional board at Auckland Hospital, and the use of radioisotopes was approved by the National Radiation Laboratory (New Zealand). The clinical details of the patients are summarized in Table 1.

Experimental Protocol

All experiments involved the infusion of isotopes and the collection of blood samples. The experiments each consisted of two periods (periods 1 and 2). At the start of period 1 a primed-constant infusion of isotopes was started and maintained for the duration of the study. In the volunteers period 1 lasted for 120 minutes, and blood samples for isotopic enrichment measurements were taken during the last 30 minutes. In the patients period 1 lasted for 180 minutes and blood samples were taken over the last 60 minutes. During the 120 minutes of period 2, in both the patients and volunteers the isotopic infusion was continued, and in addition glucose was infused at approximately 4 mg/kg/min. Blood samples were taken again during period 2. In addition, ten infusions were performed where there was no perturbation in period 2. Isotopes alone were infused throughout.

Isotopic Infusions and Calculations

In the volunteers only stable isotopes were employed, while in the patients a combination of stable and radioisotopes was used.

Glucose kinetics were determined using the primed-constant infusion of either 6,6 D2-glucose or 6-^{3}H-glucose as we have described before,[13] and glucose oxidation was measured using the primed-constant infusion of either ^{14}C-glucose or ^{13}C-glucose and appropriate priming of the bicarbonate pool.[13–15]

The primed-constant infusion of 15N-urea was used to determine urea rate of appearance in the volunteers, and in the patients similar methodology was employed using either ^{14}C- or 15N-urea. We have described this methodology previously.[13,16–19] Rates of NPC were calculated from the urea data.

Rate of appearance was calculated using the Steele equation[20] in the case of radioisotopes, and for 15N-, D2- and ^{13}C-labeled tracers the Steele equation was modified appropriately.[15–19]

Rates of NPC were calculated from the urea appearance data.[13,17,18,21]

We have previously shown that the primed-constant infusion of either ^{14}C-urea or 15N-urea to estimate urea

TABLE 2. *Metabolic Profiles of Volunteers Depleted Patients, and Cancer Patients*

	VOL	DEP	ELGI	AUGI	SARC
Glucose production (μmol/kg/min)	14 ± 1	16 ± 2	13 ± 1	18 ± 1*	28 ± 4*
Glucose clearance (mL/kg/min)	2.7 ± 0.1	3.1 ± 0.3	2.7 ± 0.3	3.4 ± 0.2*	5.4 ± 1.0*
% glucose uptake oxidized	36 ± 2	35 ± 19	38 ± 2	48 ± 6*	22 ± 2*
% glucose uptake recycled	10 ± 1	35 ± 25	6 ± 2	11 ± 5	56 ± 5*
NPC (g/kg/d)	1.4 ± 0.4	0.8 ± 0.1*	1.3 ± 0.3	2.1 ± 0.2*	3.2 ± 0.7*

* Significantly different from corresponding VOL value ($p < 0.05$ or better).

VOL = volunteers.

DEP = seven patients with depletion as a result of benign disease (peptic ulcer disease in five and inflammatory bowel disease in two).[36]

ELGI = early localized lower GI cancer.[5,6,36]

AUGI = advanced upper GI cancer.[5,6,36]

SARC = sarcoma patients.

rate of appearance in the plasma produces similar results,[16] and also that the rates of glucose appearance in plasma calculated using the primed-constant infusion of ^{14}C-glucose and ^{13}C-glucose administered simultaneously are virtually identical.[15] In addition, the rate of glucose appearance determined in volunteers using 6,6 D2-glucose is virtually identical to the value determined in nonstressed ward patients with benign peptic ulcer disease using 6-^{3}H-glucose (Table 2).

Statistical Analyses

Because there were no significant changes in either kinetic or hormonal levels between periods 1 and 2 in the control studies, the data obtained in period 2 of each study were compared with the corresponding period 1 data using a paired t-test. In addition, the data obtained in the various groups were compared using ANOVA.

Calorimetry

Rates of oxygen consumption and CO_2 production were measured using a Sybron Taylor O_2 analyzer and an ADC (Herts, England) CO_2 analyzer, as we have described previously.[13,18]

Analysis of Samples

Blood samples were immediately chilled and later centrifuged to separate the plasma.

Plasma glucose specific activity, plasma glucose enrichment, and expired air CO_2 enrichment, and/or specific activity were determined as described elsewhere.[13,15,17,19]

We have previously described the methods by which plasma ^{14}C-urea-specific activity[13,16,18] and plasma 15N-urea enrichment[16] were determined.

Serum levels of insulin and cortisol were determined by radioimmunoassay.[22,23]

Results

Calorimetry

The values for VO_2 and VCO_2 were higher in the patients than in the volunteers. The mean value of VO_2 in the volunteers was 107 ± 8 μmol/kg/min, and in the patients the corresponding value was 158 ± 12 μmol/kg/min. The basal values for VCO_2 in volunteers and patients were 80 ± 12 and 114 ± 9 μmol/kg/min, respectively ($p < 0.05$). The basal RQ in the volunteers was 0.76 ± 0.4, and in the sarcoma patients the value was similar (0.74 ± 0.4).

Insulin and Cortisol Levels

The basal cortisol concentration in the sarcoma patients was 495 ± 55 pmol/L, which was not significantly different from the locally determined value in normal humans. The basal insulin level in the patients was 7 ± 1 mIU/L and during glucose infusion this increased significantly ($p < 0.01$) to 27 ± 3 mIU/L. The basal insulin level in the volunteers was 11 ± 3 mIU/L and during glucose infusion the magnitude of the insulin response was similar to that seen in the patients. The period 2 value in the volunteers was 22 ± 7 mIU/L.

Glucose Kinetics

The basal glucose concentrations in the volunteer (VOL) group and in the patients were similar (5.2 ± 0.1 and 5.4 ± 0.3 μmol/mL, respectively). During glucose infusion the plasma glucose concentration rose significantly in both volunteers and patients ($p < 0.01$). The respective values for volunteers and patients were 7.5 ± 0.3 and 8.3 ± 0.5 μmol/mL (Fig. 1).

The basal rate of glucose appearance in the plasma in the VOL group was 13.9 ± 0.3 μmol/kg/min, and during glucose infusion there was near total suppression of endogenous glucose production. In the VOL group the rate of glucose production during glucose infusion was 0.8 ± 0.5 μmol/kg/min, and this represented a 96% suppression of endogenous glucose production. In contrast, the basal rate of glucose turnover in the sarcoma patients was significantly elevated ($p < 0.01$). The basal value for the glucose rate of appearance in the patients was 28.3 ± 3.5 μmol/kg/min and during glucose infusion there was significantly smaller suppression of endogenous glucose production ($p < 0.01$). During glucose infusion in the sarcoma patients the rate of endogenous

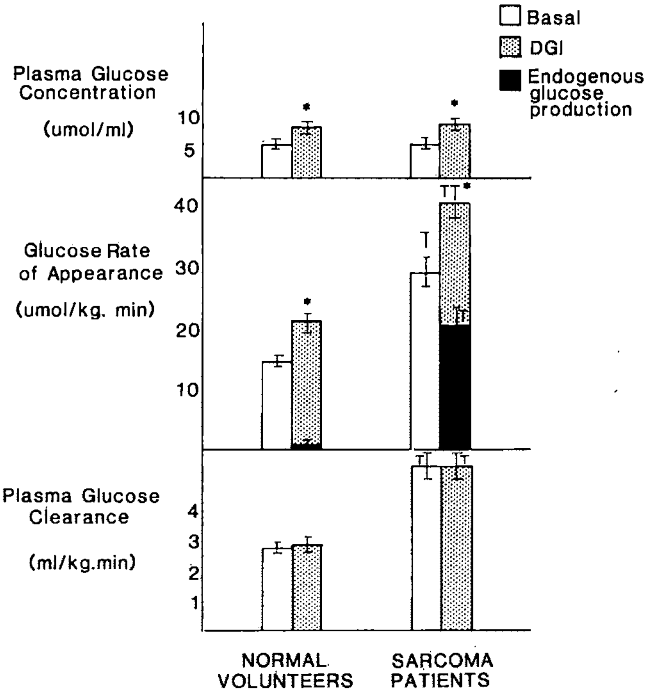

FIG. 1. Glucose kinetics in volunteers and sarcoma patients, and the response to glucose infusion. Values are given as mean ± SEM. DGI = during glucose infusion (4 mg/kg min). * Significantly different from basal value ($p < 0.01$). T, significantly different from equivalent volunteer value ($p < 0.05$).

glucose production was 20.8 ± 2.9 μmol/kg/min [significantly different from the corresponding VOL value ($p < 0.01$)]. The per cent suppression of endogenous glucose turnover in the patients was 32 ± 5 [significantly different from the VOL value ($p < 0.01$)] (Fig. 1).

The basal rate of glucose clearance in the volunteers was 2.7 ± 0.1 mL/kg/min and during glucose infusion the value was 2.8 ± 0.2 mL/kg/min. The rate of glucose clearance in the sarcoma patients was significantly greater than the corresponding VOL value, both in the basal state and during glucose infusion ($p < 0.01$). The period 1 and 2 values for glucose clearance in the patients were 5.4 ± 1.0 and 5.4 ± 1.1 mL/kg/min, respectively (Fig. 1).

The basal rate of glucose oxidation in the volunteers was 5.1 ± 0.3 μmol/kg/min, and during glucose infusion this increased to 7.2 ± 0.6 μmol/kg/min ($p < 0.01$). The rates of glucose oxidation in the sarcoma patients were higher than in the volunteers. The basal rate of glucose oxidation in the patients was 6.4 ± 0.9 μmol/kg/min and during glucose infusion the value was 9.0 ± 0.8 μmol/kg/min.

The per cent of the total VCO_2 derived from glucose oxidation in the VOL group was 25 + 3 in the basal state, and during glucose infusion 37 ± 2% of the total VCO_2 was derived from glucose oxidation ($p < 0.05$). In the patients 32 ± 2% of the total VCO_2 was derived from glucose oxidation; and during glucose infusion the value was 45 + 4%.

The per cent of glucose uptake oxidized in the VOL group in the basal state was 36 ± 2, and during glucose infusion the value was 36 ± 3%. The corresponding values for per cent glucose uptake oxidized in the sarcoma patients were significantly lower ($p < 0.05$). The period 1 and 2 values were 22 ± 2% and 20 ± 2%, respectively (Fig. 2).

The basal rate of glucose recycling in the volunteers was 10 ± 1%, and during glucose infusion this value increased to 21 ± 3%. In the sarcoma patients the basal value of glucose recycling was 56 ± 5%, and during glucose infusion the value was 55 ± 5%. These values in the patients were significantly higher than the VOL values ($p < 0.05$).

In the VOL group the basal value for urea rate of appearance was 5.7 ± 0.7 μmol/kg/min, and during glucose infusion this decreased significantly ($p < 0.02$) to 4.99 ± 0.89 μmol/kg/min. The basal value for urea rate of appearance in the sarcoma patients was significantly higher ($p < 0.01$), and in contrast to what was seen in the VOL group glucose infusion did not result in any significant suppression. The basal value in the patients was 12.6 ± 2.7 μmol/kg/min, and during glucose infusion the value was 11.9 ± 2.5 μmol/kg/min. The values for

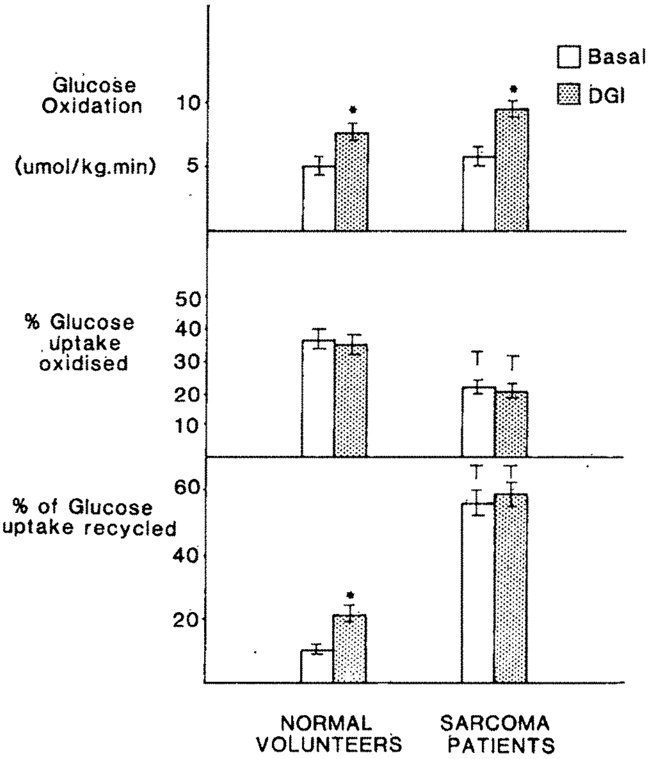

FIG. 2. Rates of glucose oxidation and glucose recycling in volunteers and patients, and the response to glucose infusion. Values are given as mean ± SEM. * Significantly greater than corresponding period 1 value ($p < 0.05$). T, significantly different from equivalent volunteer value ($p < 0.05$). DGI = during glucose infusion.

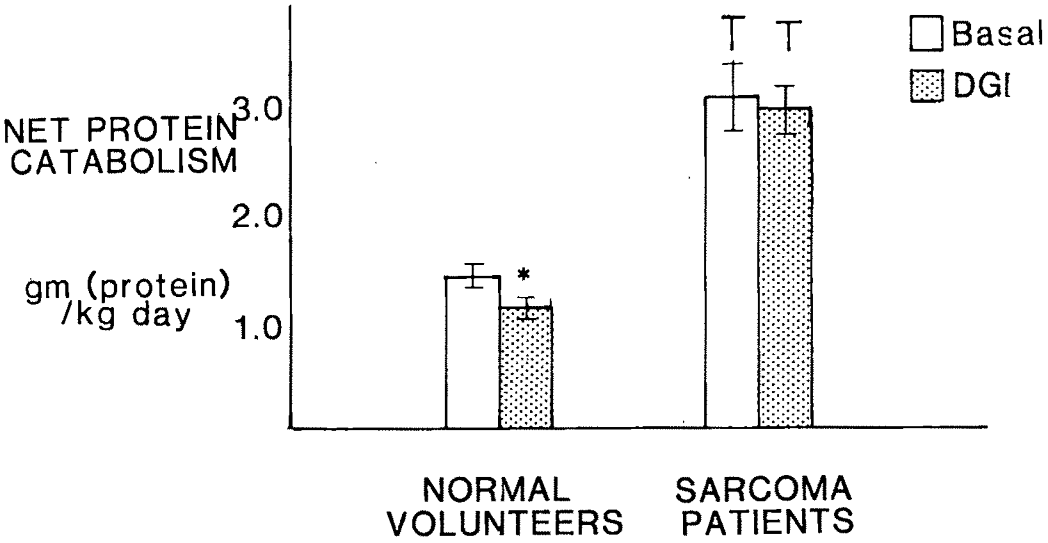

FIG. 3. NPC values in volunteers and sarcoma patients, and the response to glucose infusion. Values are given as mean ± SEM. DGI = during glucose infusion. * Significant decrease compared with basal value ($p < 0.02$). T, significantly greater than corresponding volunteer value ($p < 0.05$).

net protein breakdown were calculated from the urea turnover data. In the VOL group the values for period 1 and 2 were 1.44 ± 0.18 and 1.26 ± 0.22 g (protein)/kg/d. The corresponding values in the sarcoma patients were 3.18 ± 0.68 and 3.00 ± 0.63 g (protein)/kg/d, respectively (Fig. 3).

Discussion

In a general sense, our study confirms in the sarcoma patient a number of the abnormal findings other investigators have documented in sarcoma-bearing animals.[8-11] In addition, the extent of the metabolic derangement seen in these patients is impressive and as great in magnitude as those we have previously described in surgical patients with either trauma, sepsis, or pancreatitis.[5,6,13,17,18,24]

The mean basal value for glucose rate of appearance in the sarcoma patients (over 28 μmol/kg/min) was twice the value seen in the volunteer group (approximately 14 μmol/kg/min). In addition, this rate of glucose turnover is higher than the values we have previously described in either severe sepsis[17,25] or in pancreatitis.[13] Furthermore, the minimal suppression of endogenous glucose turnover seen in these patients during glucose infusion (30% suppression in the patients *vs.* near total suppression in the volunteers) is less than that seen in patients with GI cancer,[5] and closely resembles what is seen in critically ill patients with either sepsis[17,25] or pancreatitis.[13]

This observation of an increased rate of glucose production in sarcoma patients is in accord with the observations of a number of investigators in sarcoma-bearing animals. For example, Arbeit et al.[9] found that sarcoma-bearing rats had higher rates of glucose turnover than non–tumor-bearing rats, and Roh et al.[10] have reported that hepatocytes isolated from sarcoma-bearing rats have a significantly elevated gluconeogenic capacity and an accelerated rate of alanine transport in comparison to what was seen in hepatocytes from control animals.

The increased basal rate of oxygen consumption in the sarcoma patients is consistent with available animal data. For example, Lindmark et al.[26] observed that sarcoma-bearing mice had significantly higher rates of energy expenditure, and Roh et al.[8] have shown that hepatocytes isolated from sarcoma-bearing rats have significantly elevated rates of oxygen consumption compared with hepatocytes from control animals. Our study also provides information regarding the utilization of individual substrates in the sarcoma patients. The basal RQ in the patients was 0.74, while in the VOL group the value was 0.76. When the rate of fat oxidation is estimated from the calorimetry and NPC data using standard equations,[27] the rate of fat oxidation in the patients is 0.65 mg/kg/min *versus* 0.84 mg/kg/min in the VOL group. This lower rate of fat oxidation in the patients (compared with the VOL group), combined with the impaired capacity of the sarcoma patients to directly oxidize glucose to CO_2, indicates that the two major differences in terms of energy metabolism in the sarcoma patients were (1) an increased reliance on protein breakdown (the rate of NPC in the patients was more than twice the value determined in the VOL group), and (2) an increase in the anaerobic metabolism of glucose.

The percentage of glucose uptake that was oxidized in the patients was significantly lower than in the VOL group, and the percentage of glucose appearing in the plasma that was recycled in the patients was significantly higher. In the VOL group approximately 36% of the glucose uptake was oxidized, and 10% of the glucose appearing in the plasma was recycled, while in the patients only 22% of the glucose uptake was oxidized and 55% of the glucose appearing in the plasma was recycled.

TABLE 3. *Summary of the Alterations in Energy and Protein Metabolism Seen in Sarcoma Patients*

Basal glucose rate of appearance	Increased 100%
Plasma glucose clearance (basal and DGI)	Increased 100%
% glucose uptake oxidized (basal and DGI)	Decreased 40%
Rate of glucose recycling	
Basal	Increased 500%
DGI	Increased 250%
Metabolic rate	Increased 35%
NPC	
Basal	Increased 100%
DGI	Increased >100%
Basal plasma cortisol level	Not altered
Basal plasma insulin level and insulin response to DGI	Not altered
Suppression of endogenous glucose turnover DGI	Decreased 70%
Suppression of protein loss DGI	No suppression

The alterations are expressed as a comparison with the normal volunteer data.
DGI = during glucose infusion.

Thus, the liver of the sarcoma patient is apparently stimulated to provide a large amount of glucose, some of which is used by the tumor via anaerobic glycolysis, with lactate being recycled to the liver. This high rate of glucose recycling in the sarcoma patients is consistent with what has been documented by a variety of investigators in patients with many different types of malignant disease. For example, Cori and Cori[28] and Warburg et al.[29] demonstrated the importance of anaerobic glucose metabolism in the substrate economy of tumors in the 1920s, and more recently Waterhouse et al.[30] have demonstrated high rates of lactate turnover in patients with advanced cancer. In addition, Roh et al.[10] have shown that hepatocytes isolated from sarcoma-bearing rats have significantly elevated rates of gluconeogenesis from lactate compared with hepatocytes from control animals.

The sarcoma patients were catabolic compared with the volunteers; the basal rate of NPC in the patients was more than twice the value seen in the volunteers [approximately 3.2 *vs.* 1.4 g (protein)/kg/d]. In addition, in contrast to what was seen in the volunteers, glucose infusion did not result in any significant decrease in catabolism. This latter aspect of the response is similar to what we have previously described in patients with advanced GI cancer: an increase in NPC and no suppression following either glucose infusion[5] or isocaloric lipid infusion.[31] A number of others have documented catabolism in animal sarcoma models. Warren et al.[11] have shown that hepatocytes from sarcoma-bearing rats have significantly elevated rates of both hepatic protein synthesis and hepatic protein catabolism in comparison to controls. *In vivo* studies in animals also indicate that sarcoma-bearing is associated with catabolism. Norton et al.[32] have shown that sarcoma-bearing rats have significantly elevated rates of whole body protein catabolism, and Karlberg et al.[33] have demonstrated that sarcoma-bearing rats are in negative nitrogen balance compared with controls due to an enhanced rate of protein catabolism.

The basal insulin levels in the volunteers and patients were similar in our study, and the insulin response to glucose infusion was of similar magnitude in the two groups. These findings are in general agreement with those of Norton et al.[12] In a group of 27 sarcoma patients they found that basal insulin and glucagon levels were not significantly different from equivalent measurements in control subjects. In addition, the sarcoma patients in our study had plasma cortisol levels that were similar to those of volunteers. Thus, although cortisol is known to promote protein breakdown, induce an increase in glucose turnover, and promote substrate recycling,[34,35] it was probably not cortisol that was responsible for these changes in the sarcoma patients.

Why the sarcoma patients are so metabolically abnormal compared with volunteers, or with patients with localized lower GI cancer[5,6,36] is not completely explained by our study. It is clear, however, that sarcoma patients are more like weight-losing upper GI cancer patients in that they also have increased rates of glucose production, increased glucose clearance, increased NPC, and minimal conservation of host tissue following glucose infusion.[5,6,36] A factor common to both weight-losing GI cancer patients and sarcoma patients is the increased rate of glucose production coupled with an increased rate of glucose degradation. In the GI cancer patients this increased glucose degradation is due to an increase in aerobic glucose oxidation, while in the sarcoma patients there is an anaerobic glycolysis. When these data are considered in conjunction with the decreased rate of fat utilization seen in these two groups of patients,[6,36] it appears that a major effect of tumour bearing in these two types of cancer is the consumption of host tissue in order to meet an increased need for glucose, presumably due to increased utilization by the cancer per se either aerobically or anaerobically.[28]

These metabolic effects are clearly different from those described in simple starvation,[37] where the major changes involve a decreased reliance on glucose for energy, an increased reliance on fat, and a conservation of protein rather than an increase in protein loss as seen in weight-losing cancer. In view of the fact that we have studied a group of patients suffering from depletion as a result of benign GI disease,[36] we have compared the metabolic effects of depletion as a result of benign disease with the metabolic profile of the sarcoma patients. [We have also included the metabolic profile of the GI cancer patients for comparative purposes (Table 2)]. When these various groups of cancer patients are compared with each other, and with patients suffering from pure depletion, it is apparent that metabolically cancer patients are different from depleted patients, and that the metabolic response to tumour bearing is not uniform, but rather dependent on stage of disease, degree of weight loss, and anatomic site.

In summary, our study demonstrates that sarcoma patients display the following metabolic abnormalities in comparison to what is seen in normal volunteers: (1) an increase in metabolic rate of approximately 35%; (2) a significant increase in both glucose turnover and plasma glucose clearance; (3) the direct oxidation of glucose to CO_2 is impaired, and this is coupled with a significant increase in glucose recycling; (4) sarcoma patients have a significantly elevated rate of NPC; and (5) in contrast to what is seen in normal volunteers, sarcoma patients have a diminished capacity to conserve host resources when infused with glucose. There is no significant suppression of the elevated rate of net protein breakdown and there is less suppression of the consumption of host tissue for gluconeogenesis.

The differences between sarcoma patients and normal volunteers are summarized in Table 3, and in Table 2 the metabolic profiles of volunteers, depleted patients, and GI cancer patients are compared.

Acknowledgments

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Weight Loss with Physiologic Impairment

A Basic Indicator of Surgical Risk

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It is a long held belief that weight loss is a basic indicator of surgical risk. Many experienced surgeons, however, think otherwise. We have investigated the proposition that weight loss is a risk factor for postoperative complications but only when associated with clinically obvious physiologic impairment. Before major surgery, 102 patients had a careful history taken to ascertain if there had been recent weight loss and a reduction in the capacity for activity. Physical examination included assessment of mood, skeletal muscle function, respiratory muscle function, and wound healing. Plasma albumin was also measured. Using this information the patients were placed into one of three groups. Group I (N = 43) were normal, group II (N = 17) had weight loss > 10% but no clinical evidence of physiologic impairment, and group III (N = 42) had weight loss > 10% with clear evidence of dysfunction of two or more organ systems. The patients in group III had significantly more postoperative complications ($p < 0.05$). They also had more septic complications ($p < 0.02$) including a higher incidence of pneumonia ($p < 0.05$) and a longer hospital stay ($p < 0.05$) than patients in each of the other two groups. Objective measurements of body stores of protein and liver, and psychologic, respiratory, and skeletal muscle function, confirmed the validity of the clinical classification into the risk groups. The results demonstrate that weight loss is a basic indicator of surgical risk in modern practice providing it is associated with clinically obvious impairment of organ function. They suggest that adequate body protein stores are necessary for normal body function and for minimizing the risks of surgery.

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IN 1936 an American surgeon, Hiram Studley, claimed that "weight loss was a basic indicator of surgical risk."[1] In 50 patients undergoing gastric resection for peptic ulcer disease, he showed a striking correlation between preoperative weight loss and postoperative complications.

With advances in surgical practice, including antibiotics, physiotherapy, anesthesia and fluid and electrolyte management, this relationship can no longer be clearly demonstrated. In spite of this, many continue to cite Studley's paper[1] and claim that it proves that protein energy malnutrition is an important risk factor in modern surgery.

In our clinical practice, we have observed that weight loss does not appear to be an important risk factor for postoperative complications, unless it is associated with clinically obvious impairment of physiologic function. Preliminary work suggested to us that patients who are physiologically impaired could be identified by a thorough clinical examination,[2] and because of this we embarked on a formal prospective study to determine whether a clinical assessment of weight loss and physiologic function is able to identify patients with objective evidence of abnormal body composition and function who are also at an increased risk of postoperative complications.

Methods

Patient Selection

From April 1985 to August 1986, all patients presenting to the Department of Surgery at Auckland Hospital for elective surgical procedures, in which a major resection of some part of the gastrointestinal (GI) tract was planned, and for whom preoperative intravenous nutrition (IVN) was not considered essential, were asked if they would be willing to enter this study. On the day before surgery, the 102 patients who agreed to participate in the study underwent a clinical assessment and a series of objective tests to detect the presence of nutritional depletion and physiologic dysfunction.

Clinical Assessment of Weight Loss and Functional Status

Loss of body weight. Weight loss was evaluated from the history and physical examination. A preoperative

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weight loss (recalled well weight minus current measured weight)[3] of more than 10% over the preceding 3 months was considered significant.[4] Because there are considerable difficulties in evaluating body weight loss in an individual patient, confirmation was sought by physical examination. On physical examination, confirmation that weight loss had occurred was obtained by palpating several skinfolds and muscle bellies. If there was little or no fat palpable when subscapular, triceps, and biceps skinfolds were palpated, then it was considered that considerable fat had been lost and if on palpation of the bellies of temporalis, supraspinati, biceps, triceps, and interossei muscles revealed considerable losses, then this was taken as further evidence that considerable loss of body protein had occurred.

Functional status. The overall level of physiologic function, both mental and physical, was also assessed on history and examination. Factors that related to an overall reduction in the patient's capacity for activity (including symptoms of tiredness, malaise, depression, and apathy) were particularly looked for.[5] If there had been any major recent changes in the patient's activity level around the home or at work, this was taken as physiologic impairment.[6] Some specific physiologic functions were also assessed as part of the physical examination. To categorize a patient as having an impairment of any of these functions required clear evidence of a significant change within the time period over which the loss of weight had occurred. Psychologic function was assessed by observing the patients' overall mood, taking particular note of the alertness, ability to concentrate, and irritability. Confirmation of exercise intolerance was obtained by observing the patients' general activity level and endurance around the ward.[7] Skeletal muscle function was assessed by having the patient squeeze the examiner's hand, who then determined if the squeeze strength was clearly impaired in the light of the patient's age, sex, and body habitus.[8] Respiratory muscle function was assessed in the context of a full examination of the respiratory system, and particular note was taken of the effort and sound of coughing[9] as well as the presence of shortness of breath. Impairment of the wound healing response was evidenced by unhealed wounds, sores or scratches, and/or the presence of skin sepsis. A serum albumin concentration of less than 32 g/L was also considered a significant impairment.[2]

Categorization of Patients into 3 Groups

The patients were assessed and categorized without knowledge of any objective data, into one of three groups, by a single clinician (J.A.W.): [I] weight loss of less than 10% with no evidence of abnormal physiologic function; [II] weight loss of greater than 10% with no evidence of physiologic dysfunction; and [III] weight loss of greater than 10% with physiologic impairment of at least two of the systems described above (*i.e.*, overall activity level, psychologic function, respiratory function, skeletal muscle function, wound healing, and plasma albumin concentration).

Objective Assessment of Weight Loss and Physiologic Functions

Body composition measurements were made in order to assess the total body fat and protein stores in the three categories of patients. We were also interested in objective data to validate the clinical estimate of physiologic impairment and to this end we measured liver function, skeletal and respiratory muscle function, and psychologic function.

Anthropometry. Skinfold thickness (biceps, triceps, and subscapular) was measured using Holtain skinfold calipers, and body fat was calculated according to the method of Durnin and Wormersly.[10] Midarm circumference (MAMC), an indirect measure of body protein, was calculated as midarm circumference minus triceps skinfold thickness.[11]

Body composition analysis. Prompt *in vivo* neutron activation analysis (IVNAA) and the tritiated water dilution technique were used to measure total body protein (TBP) and total body fat (TBF).[12] The protein index,[13] a measure of protein depletion, is the measured TBP divided by a predicted TBP. The predicted TBP was derived from linear regression equations using the age, height, and sex of a local normal population who had had direct measurements of TBP. In the same way a fat index was calculated from the measured and predicted TBF, and was used to measure the extent of body fat depletion. The fat free mass (FFM) was calculated as the sum of the body water, protein, glycogen, and mineral compartments.[13]

Liver function. Plasma tranferrin and prealbumin were assayed by laser nephalometry.

Skeletal muscle function. Maximum voluntary grip strength was the highest of three values measured by isokinetic dynamometry using the dominant hand. Grip strength was also expressed as a function of the patients' FFM. Using an apparatus based on the principles of Edwards et al.,[14] the relaxation of the adductor pollicis muscle was determined in the unfatigued state after a brief tetanic stimulation (3 seconds) at 50 Hz. The relaxation time was calculated as the time taken for the force of a tetanus to fall 50% of its plateau value.[14]

Respiratory function. Respiratory muscle strength was assessed by measuring mouth pressure with a Validyne bidifferential pressure transducer (Validyne Model MP45, Validyne Engineering Corp., Northridge, CA) during maximal static inspiration (MIP) at functional residual lung capacity and during maximal static expiration (MEP) at total lung capacity.[15] A respiratory muscle strength index was derived as the average of the per cent predicted MIP and MEP. These were derived from regression equations based on the patients' age, height, and sex.[16] Forced expiratory volume in 1 second (FEVI), vital capacity (VC),[17] and peak expiratory flow rate (PEFR) were measured by standard spirometric techniques and were expressed as the percentage and predicted value derived from published regression equations.[18-20]

Psychologic function. Psychologic fatigue was measured using the Profile of Mood Score (POMS) self-questionnaire.[21]

Assessment of Clinical Course after Surgery

The clinical team responsible for each patient's postoperative care was unaware of the results of either the clinical or objective assessments. They diagnosed and recorded the complications independently and determined the date of discharge from hospital according to our usual criteria (patient up and about, eating well, and free of sepsis). The patients were also seen daily by one of us (J.A.W.) who ensured that each postoperative complication was fully documented and diagnosed according to specific clinical and laboratory criteria.

Major complications included intra-abdominal sepsis (proven by culture or abnormal drainage or at reoperation), clinically apparent anastomotic leakages, wound dehiscence (requiring reoperation), proven pulmonary emboli (requiring heparinization), pneumonia (proven by a positive blood and/or sputum culture as well as clinical and radiologic evidence of consolidation; atelectasis excluded), myocardial infarction (proved by ECG changes), cerebrovascular accidents (with neurologic deficit), and any technical problem that required the patient to undergo a further major surgical procedure. Septic complications included intra-abdominal sepsis, pneumonia, septicemia (clinical evidence of systemic infection and two separate positive cultures of the same pathogen in the absence of an obvious focus), wound infection (unequivocal signs of inflammation and a positive culture of a pathogen from the pus exuded from the wound), and urinary infection (greater than 1000 organisms/mL on culture). The number of days from operation to discharge was recorded as were all deaths that occurred within 14 days of the operation.

Statistical Analysis

Quantitative data of the three patient groups were initially evaluated with a one-way ANOVA. Multiple group comparisons of these quantitative data were done using Student's *t*-test incorporating the Bonferroni method, unless it could not be assumed that the results were normally distributed, in which case the nonparametric Kruskal-Wallis test was used.[22] Categorical data, including complication rates, were evaluated using the chi square test with Yates' correction.

Results

Patients in the 3 Clinical Categories

On the basis of the clinical assessment of nutritional and functional status 43 patients were categorized as having insignificant weight loss and normal functional status (group I), 17 patients were categorized as having significant weight loss without significant impairment of physiologic function (group II), and the remaining 42 patients were found to have significant weight loss and physiologic dysfunction as well (group III). Table 1 shows that the group III patients were, on average, older than those in the other two groups. Their average weight was also less. As might be expected, the duration of anesthesia was significantly less in the patients who had significant weight loss. It averaged 2.8 ± 1.4 (SD) hours in groups II and III compared with an average time of 3.7 ± 1.7 (SD) hours in group I $p < 0.05$. The distribution of the types of operative procedures and surgical diagnoses was similar for each of the three categories of patients, with a diagnosis of colorectal cancer in approximately half of the patients, and benign disease of the GI tract in approximately a third.

The Objective Measurement of Fat Stores, Protein Stores, and Physiologic Functions in the 3 Clinical Categories of Patients

Body stores of fat and protein together with objective measurements of function for the three clinical categories of patient are shown in Tables 2 and 3. Although the loss of body weight in groups II and III was similar (13.4% and 14.8%, respectively) and significantly more than that of the patients in group I (3.9%), body composition analysis showed that only the group III patients had body fat and protein stores that were significantly less than group I. The average deficit of body protein for the group II patients was, however, more than 20%. The combined data for the measurements of body protein and body fat in the two nutritionally depleted groups were significantly less than those for body protein (6.8 ± 0.5 kg *vs.* 8.8 ± 0.4 kg, $p < 0.001$) and body fat (13.7 ± 1.6 kg *vs.* 17.3 ± 1.2 kg, $p < .05$) in group I. The fact that there was no significant difference between the patient groups for predicted TBP and TBF indicates that there were no important differences between the groups before illness. The anthropometric measurements of body fat and MAMC confirm the three clinical categories in that groups II and III are significantly different from group I.

TABLE 1. *The Demographic Data and Surgical Diagnosis of the 3 Clinical Patient Categories*

Clinical Categories	Group I Weight Loss < 10% Normal Function		Group II Weight Loss > 10% Normal Function		Group III Weight Loss > 10% Abnormal Function	Statistical Data
Number	43		17		42	
Sex	24:18		9:8		18:24	$\chi^2 = 2.06$ (NS)
Age (yr)	60 ± 2.4	NS	61 ± 3.3	*	69 ± 2.3	$F = 7.95$ ($p < 0.005$)
			*			
Height (cm)	166 ± 1.5	NS	167 ± 1.9	NS	162 ± 1.2	$F = 3.01$ (NS)
			NS			
Weight (kg)	69.5 ± 2.3	NS	62.3 ± 2.8	*	54.6 ± 1.5	$F = 14.54$ ($p < 0.0001$)
			†			
Surgical diagnoses						
Malignant disease						
Esophagus	2		0		2	$\chi^2 = 3.09$ (NS)
Stomach	3		1		5	
Pancreas	1		0		6	
Small bowel	0		0		2	
Colon	14		8		11	$\chi^2 = 0.74$ (NS)
Rectum	4		3		6	
Benign disease						
Ulcerative colitis	5		0		1	$\chi^2 = 3.75$ (NS)
Crohn's disease	1		1		2	
Peptic ulcer disease	3		2		2	$\chi^2 = 0.16$ (NS)
Small bowel adhesions	1		1		1	
Gallstone ileus	0		0		1	
Afferent limb syndrome	0		0		1	
Chronic pancreatitis	0		0		2	
Choledochoduodenal fistula	1		0		0	
Familial polyposis	1		0		0	
Villous adenoma	2		0		0	
Diverticular disease	4		0		0	
Colonic polyp	0		1		0	

Values are given as mean ± SEM. * $p < 0.05$, † $p < 0.01$.

The objective tests of physiologic function are shown in Table 3. It is shown that nearly all the indices of liver, skeletal muscle, respiratory, and psychologic function were significantly less in group III patients, confirming that the clinical assessment and categorization of the patients in terms of clinical judgment of physiologic status has some validity.

The Postoperative Course

Table 4 shows that the patients in group III had a significantly higher incidence of major complications, septic complications, and pneumonia. Group III patients also had a longer postoperative hospital stay when compared to group II patients. The incidence of other complications shows a similar trend but does not reach the same level of statistical significance.

Discussion

Fifty years ago Studley suggested that weight loss was a basic indicator of surgical risk.[1] In modern surgical practice this appears to be only partly true since our results have demonstrated that clinically obvious physiologic impairment must be present as well. We have also shown, by sophisticated methodology, that at risk patients, identified through a careful history and examination, have in association with depleted stores of protein and fat, clear evidence of liver, skeletal muscle, and respiratory dysfunction as well as an increased perception of fatigue.

The fat and protein components of weight loss have been separately measured in this study. Preliminary work[23] had suggested to us that marked body protein loss was associated with an increased number of postoperative complications. There is probably a critical extent of body protein loss that must occur before decompensation of vital physiologic functions will result, and this may depend on such factors as the age and physical fitness of the patient, the disease, and the particular physiologic function involved. The category of patients (group III) who had significant physiologic impairment and a higher incidence of complications were signifi-

TABLE 2. *Objective Validation of the Nutritional Status of the 3 Clinical Patient Groups*

Clinical Categories	Group I Weight Loss <10% Normal Function		Group II Weight Loss >10% Normal Function		Group III Weight Loss >10% Abnormal Function	Statistical Data
Weight loss (%)	3.9 ± 0.7	†	13.4 ± 2.4	NS	14.8 ± 1.1	$F = 25.73$ ($p < 0.0001$)
			†			
Body fat stores						
Anthropometric (kg)	18.3 ± 1.1	*	13.3 ± 1.3	NS	13.7 ± 0.9	$F = 6.09$ ($p < 0.005$)
			†			
Measured TBF (kg)	17.3 ± 1.2	NS	14.9 ± 1.9	NS	13.1 ± 1.2	$F = 2.89$ (NS)
			NS			
Predicted TBF (kg)	14.7 ± 0.6	NS	14.3 ± 1.0	NS	15.6 ± 0.5	$F = 1.24$ (NS)
			NS			
Fat index (%)	117 ± 11	NS	102 ± 26	NS	84 ± 16	$F = 3.65$ ($p < 0.05$)
			*			
Body protein stores						
MAMC (cm)	264.7 ± 6.1	*	236.3 ± 6.2	NS	223.0 ± 4.9	$F = 15.66$ ($p < 0.0001$)
			†			
Measured TBP (kg)	8.8 ± 0.4	NS	7.9 ± 0.9	*	6.4 ± 0.3	$F = 8.03$ ($p < 0.005$)
			†			
Predicted TBP (kg)	9.9 ± 0.4	NS	9.9 ± 0.5	NS	9.3 ± 0.3	$F = 1.12$ (NS)
			NS			
Protein Index (%)	88 ± 3	NS	78 ± 6	NS	68 ± 3	$F = 9.67$ ($p < 0.005$)
			†			
Fat Free Mass (kg)	51.4 ± 1.9	NS	47.8 ± 2.9	NS	41.3 ± 1.5	$F = 8.42$ ($p < 0.005$)
			†			

Values are given as mean ± SEM. * $p < 0.05$, † $p < 0.01$.

TABLE 3. *Objective Validation of the Functional Status of the 3 Clinical Patient Categories*

Clinical Categories	Group I Weight Loss <10% Normal Function		Group II Weight Loss >10% Normal Function		Group III Weight Loss >10% Abnormal Function	Statistical Data
Liver function						
Transferrin (mg/100 mL)	263 ± 10	NS	247 ± 11	NS	216 ± 12	$F = 5.24$ ($p < 0.01$)
			*			
Prealbumin (mg/100 mL)	23.7 ± 1.3	NS	18.9 ± 1.5	*	13.8 ± 1.2	$F = 15.95$ ($p < 0.0001$)
			†			
Skeletal muscle function						
Grip strength (kg)	32.8 ± 1.8	NS	34.2 ± 1.9	*	22.9 ± 1.8	$F = 10.46$ ($p < 0.005$)
			*			
Grip strength/FFM (%)	65 ± 3.9	NS	70 ± 3	†	53 ± 3.3	$F = 5.56$ ($p < 0.01$)
			*			
Relaxation time (msec)	104.5 ± 2.6	NS	100.4 ± 2.8	*	116.4 ± 2.8	$F = 7.71$ ($p < 0.005$)
			*			
Respiratory function						
Respiratory muscle strength index (%)	106.9 ± 7.0	NS	98.1 ± 7.6	*	72.2 ± 8.6	$F = 3.67$ ($p < 0.05$)
			*			
FEV_1 (% predicted)	97.8 ± 3.3	NS	98.0 ± 5.7	NS	88.8 ± 5.3	$F = 1.33$ (NS)
			NS			
Vital capacity (% predicted)	108.8 ± 2.6	NS	108.7 ± 5.6	*	82.6 ± 3.6	$F = 6.35$ ($p < 0.005$)
			†			
FEV_1/VC (%)	75.9 ± 1.8	NS	78.3 ± 2.8	NS	73.8 ± 2.1	$F = 0.81$ (NS)
			NS			
PEFR (% predicted)	90.9 ± 2.5	NS	89.0 ± 4.9	*	75.2 ± 3.4	$F = 7.21$ ($p < 0.005$)
			†			
Maximum voluntary ventilation (% predicted)	81.1 ± 3.8	NS	84.4 ± 6.8	*	63.5 ± 4.3	$F = 5.66$ ($p < 0.01$)
			†			
Psychologic function						
POMS Fatigue score	5.8 ± 1.5	NS	7.5 ± 1.8	NS	9.8 ± 1.4	$H = 6.61$‡ ($p < 0.05$)
			*			

Values are given as mean ± SEM. * $p < 0.05$, † $p < 0.01$, ‡ Kruskal-Wallis statistic.

TABLE 4. *The Postoperative Course of the 3 Clinical Categories of Patients*

Clinical Categories	Group I Weight Loss <10% Normal Function	Group II Weight Loss >10% Normal Function	Group III Weight Loss >10% Abnormal Function	Statistical Data
Major complications	6	3	15	$\chi^2 = 5.98$ ($p < 0.05$)
Septic complications	8	4	18	$\chi^2 = 6.36$ ($p < 0.02$)
Pneumonia	4	1	10	$\chi^2 = 4.83$ ($p < 0.05$)
Wound infection	4	1	7	$\chi^2 = 1.79$ (NS)
Death	0	1	4	— (NS)
Hospital stay (d)	15.9 ± 1.3 ——NS——	12.7 ± 2.5 ——*——	19.2 ± 2.2	$F = 3.11$† ($p < 0.05$)
	└——————	——NS——	——————┘	

Values are given as mean ± SEM. * $p < 0.05$, † ANOVA.

cantly older, which suggests that such patients have less reserves of functioning body protein. This may account for the well-attested fact that older patients do not withstand major surgery as well as their younger counterparts.

In this study physiologic dysfunction was diagnosed only when weight loss of greater than 10% was also present. The effect on outcome of physiologic dysfunction in the patient group who had not lost this amount of weight might be considered. Only two patients in this category of 43 patients (group I) had significant physiologic dysfunction, and in both cases the dysfunction was related to chronic respiratory disease. One of these patients developed a postoperative pneumonia, while the other had an uneventful postoperative course.

Despite the large number of recommended nutritional assessment techniques (anthropometry, biochemistry, prognostic nutritional indices) that have appeared in the literature over the past 15 years,[24] no risk indicator has been shown to be superior to a careful clinical evaluation of the patient.[2,25] In an earlier study[2] we found that although a surgeon's assessment *from the end of the bed* was able to correctly identify only a small number of very high risk patients, a careful clinical assessment of medical risk, noting in particular cardiorespiratory disease and preexisting sepsis, as well as nutritional state, was as effective as any other currently used indicator of risk. It was suggested by us then that "something more than a global assessment by the operating surgeon is required to identify high risk patients."[2] In our present study we have gone one step further by formalizing a clinical assessment that includes a particular emphasis on the functional effects that are often seen in patients with a significant loss of body weight. This approach can identify a group of patients at high risk of postoperative complications. The skills required for such an assessment are no different than those taught to every student of medicine, and we have found that when the findings are carefully tabulated, interobserver agreement reaches 95% for all patient categories (unpublished observation).

In these times of escalating medical costs, preoperative nutritional repletion in hospital must be shown to be effective. Others have presented prospective data suggesting that a 10-day course of IVN given to all patients prior to major GI cancer surgery is of real benefit.[26] Our work suggests that this approach is excessive and wasteful. It would appear that only those patients who have impairment of important bodily functions in addition to significant loss of body weight should be considered for preoperative nutritional repletion. We, like others, have shown improvement in a number of important functional indices with a course of IVN,[27,28] further emphasizing the importance of body protein stores in maintaining normal body function.

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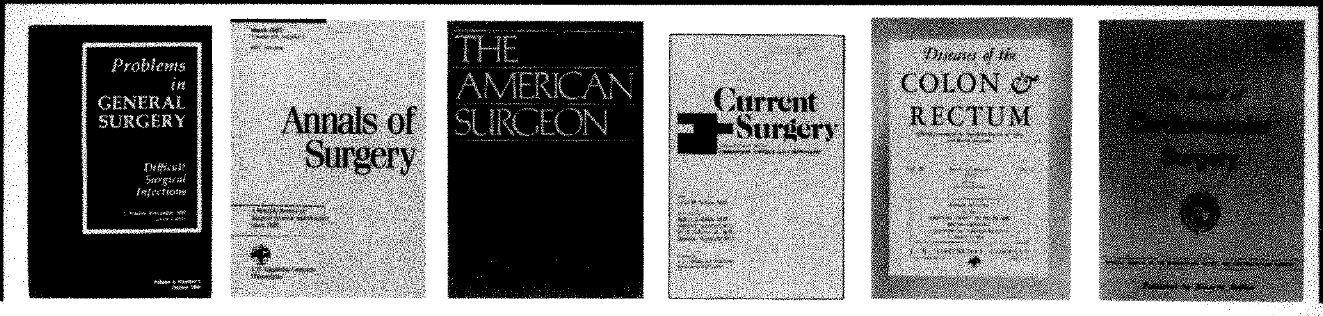
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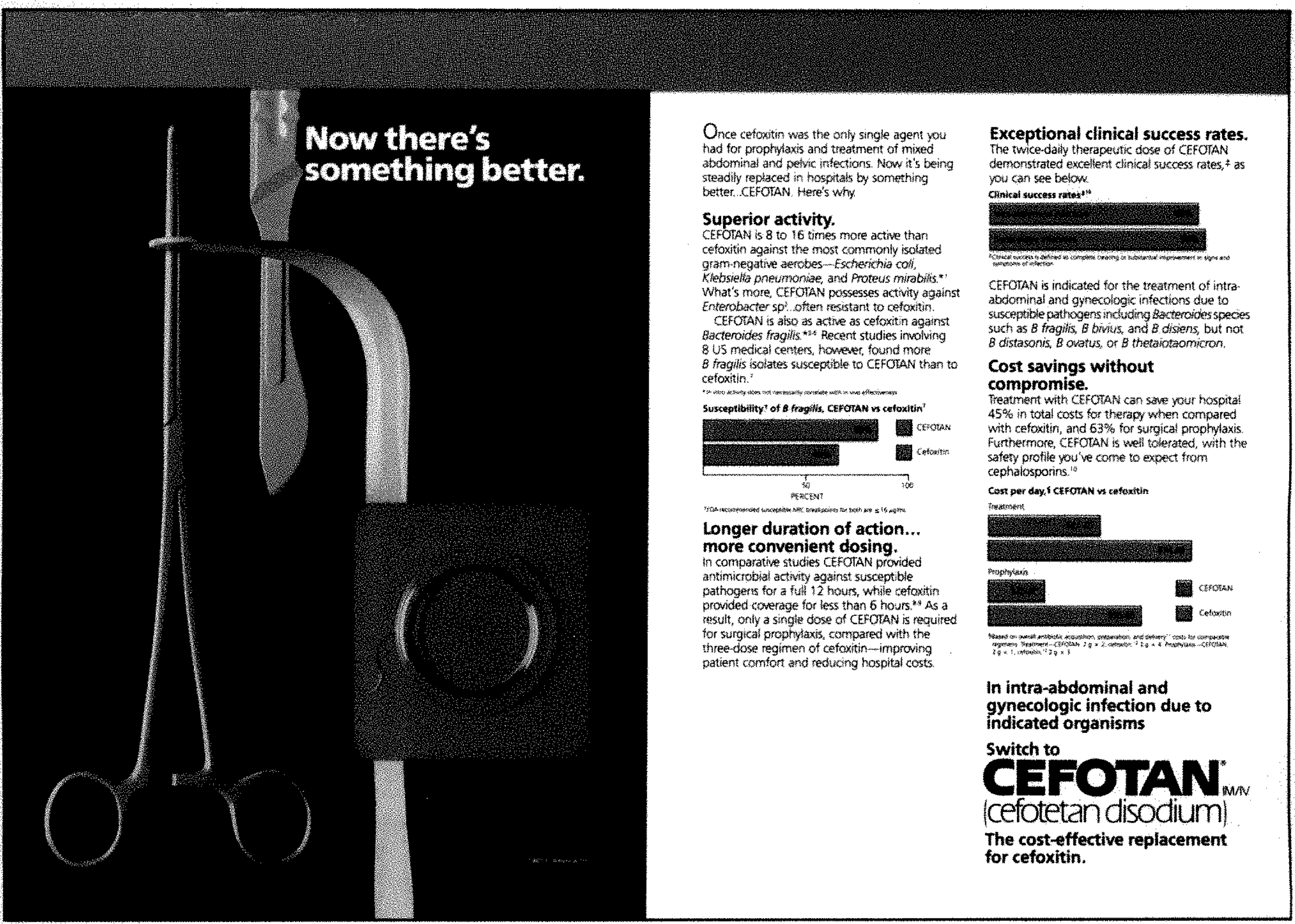

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(cefotetan disodium)

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Please see next page for brief summary of prescribing information.

In intra-abdominal and gynecologic infection due to indicated organisms

CEFOTAN® IM/IV

(cefotetan disodium)

Does so much for so much less than cefoxitin

For Intravenous or Intramuscular Use
BRIEF SUMMARY

INDICATIONS AND USAGE

TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary tract infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris*, *Providencia rettgeri*, and *Morganella morganii*).

Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.

Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.

Gynecologic infections caused by *Staphylococcus aureus*† (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus* species (excluding enterococci), *E coli*, *Proteus mirabilis*, *Neisseria gonorrhoeae*, *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*), *Fusobacterium* species,† and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species†).

Intra-abdominal infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*†), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*).

Bone and joint infections caused by *Staphylococcus aureus*.†

***NOTE:** Some strains of *Staphylococcus epidermidis* are resistant to cefotetan.

† Efficacy for this organism in this organ system was studied in fewer than ten infections.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.

PRECAUTIONS

GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state. Prothrombin times should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels of Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approx 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approx 2-4 times the usual human dose), only 1 of 10 treated animals was affected, and the degree of degeneration was mild. Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In clinical studies the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5 percent of patients: the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4 percent of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2 percent of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2 percent of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than one percent of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

DOSAGE AND ADMINISTRATION

TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dose*	Every 12 hours
10-30	Usual Recommended Dose*	Every 24 hours
<10	Usual Recommended Dose*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED

CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21)

Manufactured for

STUART PHARMACEUTICALS
Division of ICI Americas Inc
Wilmington, Delaware 19897

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Submaximal Exercise During Intravenous Hyperalimentation of Depleted Subjects

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The peripheral nitrogen wasting and loss of functional capacity caused by the malnutrition of disease and the immobilization of hospitalization may not be readily reversed by refeeding alone. In order to examine submaximal exercise as an adjunctive anabolic stimulus to intravenous refeeding (IVF) in depleted subjects, 14 volunteers were studied in the postabsorptive (PA) state, after 10 days of total starvation, and again after 10 days of nutritional repletion with I.V. feedings. The subjects were randomized to one group that received IVF alone and one group that performed 1 hour of submaximal (51% of $\dot{V}O_2$max) stationary bicycle exercise daily during IVF. The exercised group was not significantly different from the nonexercised group in urinary nitrogen balance, resting energy expenditure, extremity amino acid flux, or maximal oxygen consumption. Acute exercise did not induce significant derangements in electrolytes or counter-regulatory hormone concentrations. Ten days of submaximal exercise does not appear to be detrimental in this population recovering from moderate hospitalized malnutrition, but additional anabolic stimulae may be needed for improvements in protein accrual or functional capacity.

From the Laboratory of Surgical Metabolism and the General Clinical Research Center of the New York Hospital-Cornell Medical Center, and the Surgical Metabolism Laboratory of the Memorial Sloan-Kettering Cancer Center, New York, New York

HOSPITALIZED SURGICAL patients often suffer from progressive muscle wasting and loss of functional capacity secondary to both malnutrition and immobilization. Reversal of the poor nutritional intake alone by limited periods of adequate protein and caloric supplementation does not completely reverse these detrimental changes.[1] Since recovery from disease and early rehabilitation is thought to be associated with restoration of skeletal muscle protein stores, identification of effective stimulae for preservation and restoration of muscle mass and function would provide important adjuvants to nutritional therapy in hospitalized patients.

In isolated tissue studies and *in vivo* animal models, the stimulus that most consistently improves muscle protein balance is contractile activity.[2,3] Such activity reverses the ultrastructural changes seen with immobilization (loss of myofilaments and shrinkage of muscle fibers),[4] and may enhance protein synthesis even during unfavorable hormonal and nutritional conditions,[5] or in the presence of malignancy.[6]

Acute bouts of exercise can induce measurable changes in protein, carbohydrate, and lipid metabolism. These changes are characterized by an increase in body protein breakdown, a decrease in protein synthesis, and an increased utilization of protein for gluconeogenesis and lipids for oxidative fuel.[7-10] Chronic daily exercise, however, leads to adaptive processes that result in a net increase in total body as well as peripheral nitrogen stores.[11] Although the amount and frequency of exercise needed to bring about this adaptive process, or *training effect,* in normal humans is well studied, studies of the effects of chronic exercise in hospitalized humans are few.[12] Studies of exercise in the clinical setting of hospitalized, malnourished subjects during nutritional support are lacking.

The duration, intensity, and frequency of exercise that are needed for detectable improvements in either functional or metabolic parameters in this setting are unknown. Of perhaps equal importance is whether the acute or chronic effects of exercise in this setting would be detrimental to the subjects. These questions are important in planning physical rehabilitation of depleted patients.

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In order to assess the impact of daily submaximal exercise on protein metabolism in this setting, we studied the effects of exercise on previously starved, healthy volunteers during IVF.

Methods

Subjects

Male volunteers were screened as outpatients by complete physical exam, blood count, and serum biochemistries. Fourteen subjects aged 21–31 years and within 10% of ideal body weight for age, sex, and height (Metropolitan Life Table, 1983) were admitted to the Adult Clinical Research Center (CRC) of the New York Hospital-Cornell Medical Center (NYH-CMC). The study was approved by the Institutional Review Board of the NYH-CMC, and informed written consent was obtained from each subject prior to enrollment in the study.

Study Protocol

The volunteers were admitted to the CRC for 24 consecutive days. Subjects were weighed daily at 6:00 AM after voiding. Daily 24-hour urine samples were collected. During the first 3 hospital days, each subject was fed orally with a defined formula diet (Sustacal, Mead-Johnson, Evansville, IN) in six equal portions daily. This diet was provided at 1.2 times the resting energy expenditure (REE) (33 ± 2 kcal/kg/d, 0.32 ± 0.01 gN/kg/d). Feedings were discontinued at 8:00 PM on hospital day 3 and at 7:00 AM on day 4, in the postabsorptive (PA) state; measurements of REE and extremity substrate flux were performed as outlined below.

From hospital days 4 to 14, a 10-day protein-calorie starvation period was achieved during which oral intake was limited to distilled water, no-calorie soft drink (provided *ad libitum*), and a tablet of sodium chloride (20 mEq/d). At 7:00 AM on hospital day 14 measurements of REE and substrate flux were repeated in the starvation (STV) state. A percutaneous catheter was then inserted into the antecubital vein and advanced into the superior vena cava (placement confirmed by chest roentgenography). All subjects received I.V. feeding from hospital days 14–24 with a commercially available amino acid source (aminosyn, 5%) and 100% of the nonprotein calories as D-glucose. The nutrients provided were 30 ± 2 nonprotein kcal/kg/d and 0.30 ± 0.02 gN/kg/d. Appropriate electrolytes, trace metals, and vitamins were added by previously described standards.[12]

From the time of admission until day 14 all subjects were allowed to ambulate within the ward but were restricted from any other physical activity. After beginning IVF the subjects were randomly selected to enter one of two physical activity groups. One group (−EX) (N = 7) continued to be restricted from any physical activity other than light ambulation within the hospital ward, while the other group (+EX) (N = 7) underwent 1 hour of daily upright bicycle exercise (Monarch Corp., Stockholm) at 51 ± 3% of $\dot{V}O_2$max. The exercise was performed between 5:00 PM and 6:00 PM each day during the I.V. feeding. On day 3 of the exercise regimen venous plasma electrolyte, glucose, catecholamine, glucagon, and cortisol levels were determined at 20-minute intervals during the 1-hour exercise period and at half-hour intervals for 1 hour after the exercise period.

On day 24 at 7:00 AM REE and substrate flux measurements were again made, this time under IVF conditions. On days 3, 13, and 23, maximal oxygen uptake ($\dot{V}O_2$max) determinations as described below were also made at least 12 hours before each metabolic study session.

Urinary Nitrogen Balance

Daily 24-hour urine collections were made. The samples were refrigerated and treated with sodium fluoride during collection and then frozen at −70 C immediately until analysis. After digesting the samples using a micro-Kjeldahl method, the total nitrogen was analyzed using the Technicon AutoAnalyzer-2 (Technicon, Tarrytown, NY). Urinary nitrogen balance was calculated as previously described.[13]

REE

Measurements of oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were performed in the supine position with a Beckman Metabolic Measurement Cart-1 (Sensormedics Corp., Anaheim, CA). This system contained an OM-11 oxygen analyzer and LB-2 carbon dioxide analyzer. The instrument was calibrated before and after each test using a minimum of two standard calibration gases (100% nitrogen, and 16%:4% oxygen:carbon dioxide).[14] REE was estimated using the de V. Weir formula [REE(cal/min) = $3.941 \times \dot{V}O_2 + 1.106 \times \dot{V}CO_2$].[15]

Extremity Substrate Flux

Percutaneous radial artery and retrograde venous catheters (basilic or femoral) were placed on days 4, 14, and 24. Arterial and venous samples for substrate analysis were drawn simultaneously from the catheters. Blood flow to the extremity was determined before and after the blood sampling using electrocapacitance plethysmography.[16] Four of the nonexercised subjects had leg flux determinations while three had nondominant arm flux determinations. All exercised subjects had determinations of leg substrate flux only. Plasma amino acid flux was calculated as (arterial concentration − venous concentration) × blood flow × (1 − hematocrit). A posi-

TABLE 1. *Anthropometric Data and Liver Function Tests*

	PA	STV	IVF
Age (yr)			
−EX	28 ± 2	—	—
+EX	26 ± 1	—	—
Weight (kg)			
−EX	80 ± 3	73 ± 3 (−8% *vs.* PA)	78 ± 2 (−3% *vs.* PA)
+EX	73 ± 3	68 ± 2 (−7% *vs.* PA)	72 ± 2 (−2% *vs.* PA)
Albumin (g/dL)			
−EX	4.2 ± 0.1	4.1 ± 0.1	4.0 ± 0.1
+EX	4.2 ± 0.1	4.1 ± 0.1	4.0 ± 0.1
Alkaline phosphatase (U/L)			
−EX	66 ± 2	64 ± 4	60 ± 5
+EX	59 ± 6	58 ± 8	56 ± 3
Bilirubin (mg/dL)			
−EX	0.8 ± 0.1	1.1 ± 0.2	0.5 ± 0.2
+EX	0.6 ± 0.1	0.9 ± 0.3	0.6 ± 0.2
SGOT (U/L)			
−EX	29 ± 6	17 ± 3	41 ± 13
+EX	24 ± 4	17 ± 1*	28 ± 2†
Glucose (mg/dL)			
−EX	92 ± 3	60 ± 1*	107 ± 5*†
+EX	100 ± 8	69 ± 6*	107 ± 2*†

Values are given as mean ± SEM
* $p < 0.05$ *versus* PA.
† $p < 0.05$ *versus* STV.

tive value represents a relative uptake across the extremity whereas a negative value indicates a net efflux of amino acids out from the extremity.

Substrate Concentrations

Plasma amino acids, including glutamine,[17] were determined by column chromatography on a Beckman 119CL amino acid analyzer (Beckman Instruments, Fullerton, CA) using a three-buffer lithium system with ethyl-cysteine as an internal standard.[18] Cortisol was measured by radioimmunoassay.[19] Plasma for glucagon was collected with EDTA and aprotinin prior to analysis by radioimmunoassay.[20] Epinephrine, norepinephrine, and dopamine levels were determined by radioenzymatic assays.[21]

Blood count, electrolytes, glucose, and liver function tests were analysed using standard automated techniques available in the NYH-CMC Clinical Biochemistry Laboratories.

$\dot{V}O_2max$

$\dot{V}O_2$max was determined by stepwise bicycle ergometry (25–125 watts) using the linear relationship between $\dot{V}O_2$ and heart rate.[22] Subjects underwent continuous heart rate monitoring by ECG and $\dot{V}O_2$ determinations every 30 seconds for the study. Heart rate and $\dot{V}O_2$ were determined under basal conditions and during 4-minute intervals of incremental submaximal exercise. Mean heart rates (y axis) were plotted against $\dot{V}O_2$ (x axis) and linear regression analysis performed for each study. Using 220 − age as an estimated maximal heart rate,[23] $\dot{V}O_2$max was calculated as:

$$[(220 - \text{age}) - y \text{ intercept}]/\text{m},$$

where m is the slope of the linear regression line of the heart rate against $\dot{V}O_2$ under basal and submaximal exercise conditions.

Statistical Analysis

All data are expressed as mean ± SEM. Standard paired and unpaired Student's t-tests were used for single comparisons. ANOVA and Newman-Keuls tests, where appropriate, were used to identify statistical significance for multiple comparisons.

Results

Patient Groups

The average age of the volunteers in the exercised group was comparable to that in the nonexercised group (Table 1). The volunteers randomized to the nonexercised regimen had a higher average initial weight than those randomized to the exercise program (80 ± 3 kg *vs.* 73 ± 3 kg). However, both groups lost a similar per cent of body weight with 10 days of starvation (−8% *vs.* PA and −7% *vs.* PA). Both groups also exhibited similar weight recovery during IVF, reaching within 3% of initial weight in nonexercised subjects and 2% of initial weight in exercised subjects (Table 1). Thus, both groups demonstrated similar levels of depletion and subsequent repletion with the experimental regimen.

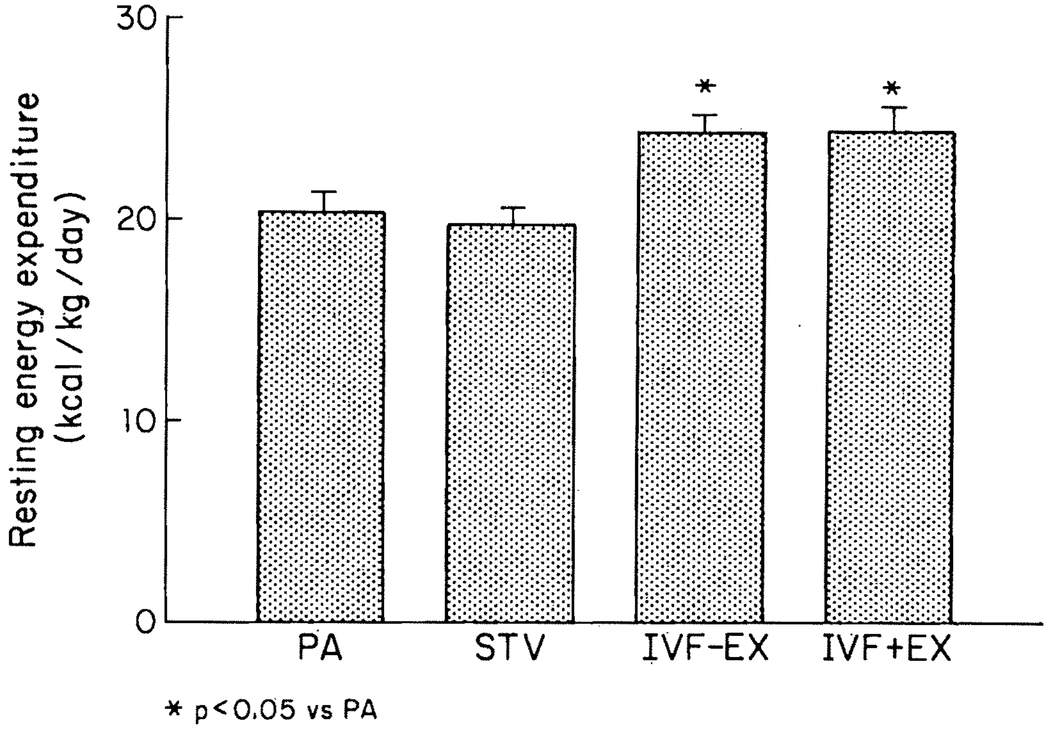

FIG. 1. REE was determined in the PA (N = 14), STV (N = 14), I.V. feeding without daily exercise (IVF − EX) (N = 7), and I.V. feeding with daily exercise (IVF + EX) (N = 7) conditions.

Serum Chemistries

Serum albumin levels were not significantly changed throughout the course of the experiment and were comparable in the exercised and nonexercised groups (Table 1). In agreement with previous reports, glucose levels decreased after 10 days of starvation and then rose during refeeding with the glucose-based parenteral feeding.[24] The values for both groups remained within the normal range for liver function tests throughout the study and were not statistically different between the groups.

REE

The REE was similar in the PA and the STV states (20.4 ± 0.9 and 19.8 ± 0.8 kcal/kg/d) (Fig. 1). REE rose significantly with IVF to 24.4 ± 0.9 in the nonexercised group and 24.5 ± 1.0 in the exercised group (both $p < 0.05$ *vs.* PA).

Urinary Nitrogen Balance

Negative nitrogen balance in the PA state (−0.12 ± 0.01 gN/kg/d) decreased significantly after starvation (−0.095 ± 0.009 gN/kg/d), indicating a degree of nitrogen sparing with starvation (Fig. 2). This is similar to levels previously reported in starved man.[13,25] With IVF both the exercised and nonexercised groups reached positive nitrogen balance by the second day of I.V. feeding. There were no significant differences of nitrogen balance between the two groups throughout the course of the study [0.12 ± 0.01 in the nonexercised (−EX) group and 0.11 ± 0.01 gN/kg/d in the exercised (+EX) group].

Extremity Amino Acid Flux

The total amino acid flux (TAA) across the extremity in the PA state was −950 ± 150 nmol/min/100 mL tissue (Table 2), similar to previous reports.[1] With starvation, efflux decreased to −700 ± 160 nmol/min/100 mL tissue, suggesting nitrogen sparing within the extremity. With refeeding, TAA flux in the group randomized to the exercise regimen and the group randomized to the nonexercise regimen, both rose significantly, to −39 ± 48 and +30 ± 160, respectively, but not statistically different between the two groups.

Only the flux of the amino acids serine and methionine showed significant differences between the exercised and nonexercised groups during IVF. All other amino acids, either alone or grouped as essential amino acids (EAA), branched chain amino acids (BCAA), or glutamine and alanine (G + A) were without significant differences in flux between the two groups during IVF (Fig. 3).

$\dot{V}O_2$

The group randomized to nonexercise had an initially higher $\dot{V}O_2$max (35 ± 1 mL/kg/min) than the group chosen to exercise (30 ± 3 mL/kg/min) (Fig. 4). Both groups demonstrated a similar percentage decline in $\dot{V}O_2$max with starvation (−10% *vs.* PA and −11% *vs.* PA). With IVF both groups showed a similar further

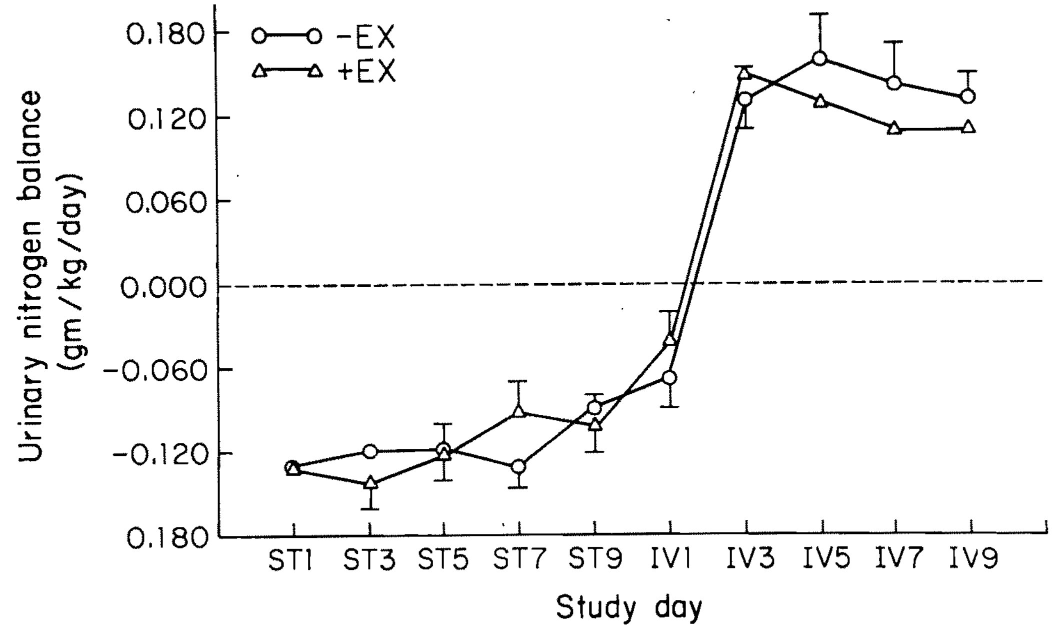

FIG. 2. Urinary nitrogen balance in exercised (+EX) and nonexercised (−EX) subjects. The data are plotted during ST and during IVF. Results are given as means ± SEM. There were no statistically significant differences between the two groups.

percentage decline in $\dot{V}O_2$max to −20% and −22% compared with the PA values.

Acute Electrolyte and Hormonal Changes with Exercise

There were no statistically significant changes in electrolyte or glucose levels during or immediately after an exercise session during IVF (Table 3). Venous epinephrine and dopamine levels rose significantly during the exercise session but remained in a low range and returned to pre-exercise levels within 1 hour of exercise. Serum concentrations of cortisol, glucagon, and norepinephrine also demonstrated slight increases during exercise, but these increased levels were not statistically different from baseline.

Discussion

It is estimated that 50% of all hospitalized patients exhibit overt clinical signs of malnutrition.[26] It is frequent in the surgical population, whether because of underlying disease or surgical procedures, that patients undergo periods of fasting and hospitalized immobilization. Significant total body and peripheral protein wast-

TABLE 2. *Extremity Amino Acid Flux*

	PA	STV	IVF − EX	IVF + EX
Taurine	4 ± 6	4 ± 2	−2 ± 3	4 ± 4
Aspartate	3.0 ± 0.4	0.9 ± 0.5*	3.3 ± 0.8†	2.6 ± 1.8
Threonine	−48 ± 8	−32 ± 12	15 ± 16*†	−14 ± 7*
Serine	11 ± 3	−20 ± 9*	44 ± 12*†	8 ± 6†‡
Asparagine	−54 ± 23	−31 ± 7	−23 ± 10	−14 ± 16
Glutamate	81 ± 31	57 ± 11	102 ± 36	114 ± 34
Glutamine	−321 ± 55	−200 ± 50	−187 ± 67	−101 ± 33*
Proline	−131 ± 20	−27 ± 21*	23 ± 62*	−16 ± 20*
Glycine	−65 ± 9	−73 ± 21	−55 ± 31	−51 ± 20
Alanine	−271 ± 39	−143 ± 25*	−137 ± 40*	−174 ± 57
Valine	−20 ± 8	−26 ± 19	79 ± 25*†	35 ± 17*
Cysteine	12 ± 5	3 ± 7	2 ± 2	5 ± 2
Methionine	−10 ± 3	−15 ± 3	6 ± 3*†	−1 ± 1*†‡
Isoleucine	−11 ± 2	−22 ± 7	53 ± 11*†	22 ± 10*†
Leucine	−17 ± 5	−46 ± 12*	59 ± 9*†	35 ± 11*†
Tyrosine	−17 ± 2	−16 ± 3	5 ± 2*†	1 ± 1*†
Phenylalanine	−15 ± 3	−17 ± 4	8 ± 3*†	1 ± 2*†
Ornithine	2 ± 1	−3 ± 4	21 ± 5*†	5 ± 8
Lysine	−53 ± 8	−72 ± 19	30 ± 14*†	15 ± 11*†
Histidine	−21 ± 4	−15 ± 5	−2 ± 3*	−1 ± 3*
Arginine	−24 ± 8	−26 ± 7	27 ± 11*†	17 ± 10*†

A positive value indicates uptake into the extremity while a negative value indicates efflux of amino acids from the extremity.

* $p < 0.05$ *versus* PA.

† $p < 0.05$ *versus* STV.

‡ $p < 0.05$ IVF − EX *versus* IVF + EX.

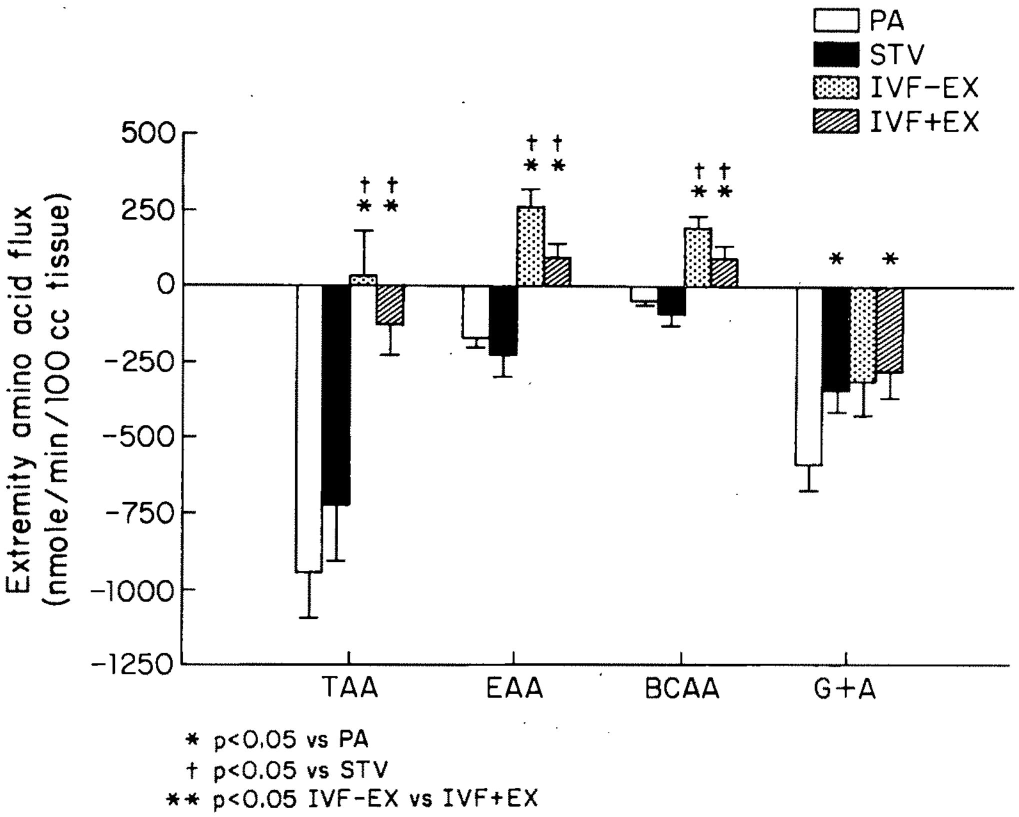

FIG. 3. Extremity amino acid flux of TAAs, EAAs, BCAAs, and the sum of glutamine and alanine (G + A). Measurements were performed in the PA, STV, I.V. feeding without daily exercise (IVF − EX), and I.V. feeding with exercise (IVF + EX) conditions. A positive value indicates extremity uptake of amino acids and a negative value indicates an efflux of amino acids from the extremity.

ing can be seen after as little as 4 days of in-hospital bed rest.[27]

Previous studies have examined the efficacy of chronic submaximal exercise used in conjunction with I.V. alimentation in reversing the negative effects of hospitalized immobilization.[12,28] In those studies, daily submaximal exercise in hospitalized but well nourished volunteers was observed to be associated with improve-

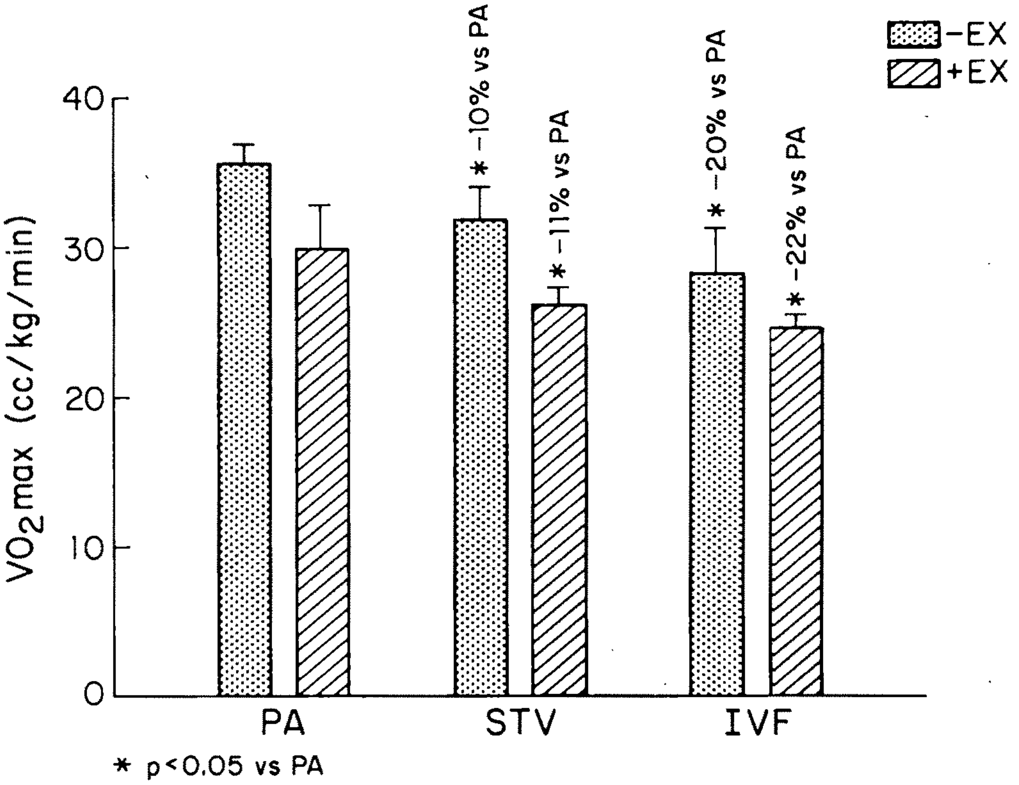

FIG. 4. Maximal oxygen uptake measured during PA, STV, and IVF conditions. The data are presented for nonexercised (−EX) and exercised (+EX) subjects. The per cent change *versus* the PA condition is indicated above the bars.

TABLE 3. *Hormone and Electrolyte Levels during and Immediately after Exercise*

	Baseline	20 Minutes	40 Minutes	60 Minutes	90 Minutes	120 Minutes
Glucagon (pg/mL)	104 ± 28	154 ± 38	165 ± 33	140 ± 33	109 ± 19	132 ± 16
Cortisol (ng/ml)	10 ± 3	10 ± 2	11 ± 2	13 ± 2	11 ± 2	10 ± 2
Epinephrine (pg/ml)	45 ± 3	127 ± 24*	100 ± 18*	132 ± 32*	69 ± 20	84 ± 25
Norepinephrine (pg/mL)	590 ± 250	1740 ± 660	1760 ± 860	1520 ± 490	490 ± 160	570 ± 230
Dopamine (pg/mL)	21 ± 3	47 ± 10*	54 ± 12*	99 ± 30*	25 ± 4	27 ± 7
NA	140 ± 1	142 ± 1	139 ± 1	139 ± 1	139 ± 1	139 ± 1
K	4.5 ± 0.1	4.7 ± 0.1	4.8 ± 0.2	4.7 ± 0.1	4.8 ± 0.1	4.6 ± 0.1
CL	106 ± 1	107 ± 1	107 ± 1	107 ± 1	107 ± 1	107 ± 1
CO_2	26 ± 1	22 ± 1*	22 ± 1*	23 ± 1	25 ± 1	25 ± 1
Glucose	106 ± 9	93 ± 16	93 ± 10	94 ± 9	97 ± 10	101 ± 9

Exercise was performed after the baseline (BL) measurements and continued through the 60-minute measurements. The subjects then rested for the 90- and 120-minute measurements.

* $p < 0.05$ *versus* baseline.

ments in total body and extremity nitrogen balance. The effects of such an exercise regimen, however, in the clinically relevant setting of immobilization compounded by malnutrition remained uncharacterized.

Since the amount of training improvement is known to be inversely related to the prior fitness level,[29] employing an untrained population allows the best opportunity for detecting any improvement brought on by the exercise regimen. Therefore, we chose to examine chronic submaximal exercise as an adjunct to IVF in a disease-free volunteer population subjected to hospitalized immobilization and malnutrition. The selection of healthy volunteers avoids the confounding variability inherent to comparisons of patients with different illnesses and differing degrees of stress-induced hypermetabolism.

The level of exercise in this study was chosen for its potential clinical applicability. It has been demonstrated[30] that this level of exercise has been able to bring about a training effect in well-nourished volunteers. It is also the most vigorous regimen that we thought can be reasonably expected of an ill, hospitalized, and possibly postsurgical population. However, 10 days of daily submaximal exercise at this intensity did not improve the total body or peripheral nitrogen accrual in the current study population.

We did verify that adequate nutritional supplementation via the I.V. route is able to abate the total body and peripheral nitrogen losses seen in otherwise unstressed but malnourished hospitalized subjects. While this supplementation is sufficient in promoting total body nitrogen accrual, we did not observe any net muscle-specific amino acid uptake.

Hospitalized patients demonstrate a progressive loss of functional capacity as measured by $\dot{V}O_2$max,[11] and this loss in functional capacity can be detected within 4 days.[27] Since early rehabilitation and return to premorbid and useful activity is thought to be facilitated by a preservation of functional capacity, methods of preserving or improving functional capacity have long been investigated. It has been demonstrated that nutritional supplementation alone, either in the form of hypocaloric glucose or amino acid supplementation,[31,32] was not effective in preserving functional capacity in postoperative patients. Intravenous hyperalimentation alone in hospitalized volunteers was also not effective in preserving functional capacity.[12]

The current study demonstrates that the immobilization of hospitalization and malnutrition are sufficient stimulae in bringing about a decline in $\dot{V}O_2$max. The degree of change is similar to a previous report of the change in $\dot{V}O_2$max in an otherwise healthy volunteer population subjected to 20 days of bed rest alone without depletion.[33] In contrast to nondepleted subjects, however, the current study shows that 10 days of chronic submaximal exercise was not adequate in previously depleted subjects of alleviating the further detraining effects of hospitalization, even in the setting of adequate I.V. repletion. The REE, which is related to physical conditioning,[34] also demonstrated no detectable difference between the exercised and nonexercised groups at the end of the IVF period.

It is important to note that the exercise regimen explored in the current study did not produce significant acute or chronic detrimental effects in this population during refeeding. Previous investigators observed that unfed normal volunteers may develop hypoglycemia during acute exercise.[35] Counter-regulatory hormone rises have been observed with exercise and seem to be inversely related to the subject's level of physical conditioning.[36] Therefore, it is a legitimate concern that physical activity in a depleted, detrained population such as this may cause intolerable, detrimental hormonal or substrate changes. The present data, however, show that potassium and glucose levels remained unchanged during acute exercise and counter-regulatory hormone changes were acceptably small during the bouts of exercise. This suggests that the acute effects of exercise at the current level were well tolerated in this setting of recovery from the fasting-induced catabolic state. The cumulative effects of the 10 days of submaximal exercise also did not seem detrimental to the subjects in any of the measured parameters. Thus, mobilization and physical rehabilitation might safely be initiated early in the recovery from hospitalization and moderate malnutrition.

Since training improvement seems to be directly related to training intensity and duration,[29] perhaps a higher level of exercise, longer daily bouts of exercise, or more days of exercise will produce detectable benefit in this population. Higher levels of exercise or longer bouts, however, are probably not clinically applicable options.

In summary, IVF in the setting of hospitalized immobilization was able to restore total body protein but was less successful in restoration of skeletal muscle mass. The addition of 10 days of daily submaximal exercise did not significantly impact upon the peripheral accrual of nitrogen in this previously depleted population. Therefore, additional anabolic stimulae might be used in an adjuvant setting both to affect earlier restoration of lean body mass as well as to supplement the functional response to submaximal exercise.

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Financial Risk, Hospital Cost, Complications, and Comorbidities in Surgical Noncomplication- and Noncomorbidity-stratified Diagnostic Related Groups

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The purpose of this study was to analyze resource consumption in the 147 non-complicating condition–stratified surgical diagnostic related groups (DRGs). Analysis of 2647 surgical patients in these non-CC–stratified surgical DRGs demonstrated that patients with more CCs per DRG generated higher total hospital costs, a longer hospital length of stay, a greater percentage of procedures per patient, financial risk under DRG payment, more outliers, and a higher mortality rates than patients in these same DRGs with fewer CCs. These findings suggest that the current DRG classification system may be inequitable to certain groups of patients or types of hospitals vis-à-vis the non-CC–stratified surgical DRGs. Financial disincentives to treat these patients may affect both their access and quality of care in the future.

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MEDICARE'S NEW Diagnostic Related Group (DRG) hospital payment system has introduced financial risk for hospitals treating certain groups of patients.[1,2] Some hospitals, such as teaching or public hospitals, which treat a more severely ill patient or more emergency admissions, may be underreimbursed by DRGs for the greater cost of these patients.[3,4] DRGs were constructed to consider some factors that contribute to higher hospital expenses per patient. Surgical DRGs are grouped in an attempt to provide appropriate reimbursement to hospitals based on the type of operative procedure. Some surgical DRGs are stratified for a given operation for patients who have complications or comorbidities. These patients receive higher DRG reimbursement. At the present time 147 of the 250 surgical DRGs (58.8%) are *not* stratified by the presence or absence of a complication (*i.e.*, a condition present after admission to the hospital) or a comorbidity (*i.e.*, a condition present on admission to the hospital).[5] The purpose of this project was to analyze resource consumption in the noncomplication- and noncomorbidity-stratified surgical DRGs, and to test the hypothesis that financial risk would be generated by patients who had a greater number of CCs in these DRGs.

Methods

All Medicare surgical patients (N = 2647) admitted to the Long Island Jewish Medical Center (an 805-bed teaching hospital in suburban New York City) in any of the 147 non-CC–stratified surgical DRGs from January 1, 1985 to December 31, 1986 were studied. Our hospital is categorized as an urban teaching hospital by the DRG reimbursement scheme; standard New York State DRG methodology was used for this analysis. All general surgery and surgical subspecialty patients (*e.g.*, ENT, orthopedic, neurosurgery, *etc.*) in these non-CC–stratified DRGs were studied. The assessment of CCs was calculated by the number of ICD-9-CM diagnostic codes (as a proxy for CCs) per patient. Patients with only one ICD-9-CM code were grouped as having no CCs; patients with two ICD-9-CM codes, one CC; patients with three ICD-9-CM codes, two CCs; *etc.* Patients were grouped into four categories: all patients with no CCs, all patients with 1 or 2 CCs, all patients with 3 or 4 CCs, and all patients with over 4 CCs.

Hospital costs for each CC group (exclusive of MD fees) were computed for each patient by hospital service area to include the following: room and board, laboratory (urinalysis, hematology, coagulation, biochemistry, and microbiology), radiology, blood and blood products, operating room/recovery room, central supply/pharmacy, and other (ECG, pathology, respiratory therapy, *etc.*). A number of characteristics were analyzed for

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TABLE 1. *Cost to Charge Ratios Used to Convert Charges to Costs*

Service Category	Ratio
Room and board	0.75
Laboratory	0.40
Blood (storage, processing, transfusion, and products)	1.15
Pathology	2.42
Diagnostic radiology	0.94
Therapeutic radiology	1.71
Operating room	1.10
Recovery room	1.15
Respiratory therapy	0.76
Electrocardiology	0.25
Electroencephalography	1.40
Medical supplies	1.00
Pharmacy	1.00
Diagnostic ultrasound	0.46
Computed tomographic scan	0.53
Emergency department	0.91
Pulmonary function	0.08

each patient including mean total hospital cost per patient, mean hospital cost per patient for each hospital service, mean DRG reimbursement per patient, mean profit/loss per patient, mean hospital length of stay (LOS) per patient, the mean number of diagnostic codes (ICD-9-CM) per patient, the mean number of procedure codes (ICD-9-CM) per patient, the per cent outliers, and mortality rates. In addition, four clinical characteristics were analyzed for each CC category such as surgical intensive care unit (SICU) admission, the requirement for plasma products (*i.e.*, blood products), need for blood transfusion (*i.e.*, red cells), and the need for emergency (ER) admission. The ANOVA was used to test for statistical significance between groups of patients. Linear regression analysis was performed to test the relationship between total hospital cost *versus* the number of CCs per patient. In order to account for per patient differences in DRG weight index, the linear regression equation was total hospital cost per patient/DRG weight index per patient *versus* number of CCs per patient.

Hospital Costing Methodology

Hospital cost per patient was obtained by utilizing per patient charge specific data and converting these charges to hospital costs. Cost to charge ratios utilized by our hospital accounting division were used to convert charges to costs. The ratios used for each hospital service category are listed in Table 1. To obtain the hospital cost for diagnostic radiology of \$100, the following calculation was performed (\$100 × 0.94 = \$94); medical supplies (\$100 × 1.00 = \$100); blood (\$100 × 1.15 = \$115); and so on.

Results

The mean DRG weight index per patient for all 2647 patients was 1.9198 (Table 2). Mean DRG weight index per patient rose as the number of CCs per patient increased; highest was for patients with over 4 CCs per patient, 2.7554. This relative increase in DRG weight index with increasing CCs should be kept in mind as resource consumption per patient is analyzed. Patients with over 4 CCs per patient had a 193% greater mean DRG weight index than patients with no CCs per patient. Mean hospital LOS per patient for all patients was 12.5 days; highest hospital LOS was for patients with over 4 CCs per patient, 29.5 days (a 447% greater hospital LOS than for patients with no CCs). The mean profit per patient under DRG reimbursement was \$419; patients with over 4 CCs, however, generated a \$9,556 loss per patient (\$3,812,844 aggregate loss for these patients). The mean number of diagnoses per patient for all patients was 3.17, and the mean number of procedures per patient 2.73. The number of procedures increased as CCs accumulated.

The mean total hospital cost per patient for all patients was \$11,271. Mean hospital cost increased as CCs per patient rose; highest hospital cost per patient was for patients with over 4 CCs, \$27,157 (a 436% greater cost than for patients with no CCs). In order to equilibrate the effect of DRG weight index for cost per patient, a ratio was computed of mean hospital cost per patient divided by the DRG weight index per patient for each CC category. This ratio was as follows: no CCs, 4,360; 1 or 2 CCs, 4,692; 2 or 3 CCs, 5348; and over 4 CCs, 9,855. Thus *relative* hospital cost per patient rose (keep-

TABLE 2. *Surgery: Non-CC–Stratified DRGs Resource Characteristics by CCs*

CC Category	Sample Size	DRG Weight Index	Costs Weight/Index*	Hospital LOS (d)	Profit/Loss (\$)	No. of Diagnoses‡	No. of Procedures‡
None	745	1.4276§	4360	6.6§	2585§	1.00§	1.77§
1 or 2	1023	1.8586	4692	9.8§	2368§	2.42§	2.41§
3 or 4	480	2.1197§	5348	13.3	1279	4.43§	3.05§
Over 4	399	2.7554§	9855	29.5§	(9556)§	7.66§	4.99§
All	2,647	1.9198	5871	12.5	419	3.17	2.73

Values are given as mean per patient.

* Mean total hospital cost per patient divided by DRG weight index per patient.

† (ICD-9-CM) codes per patient.

‡ Mean profit/loss per patient; values in parentheses pertain to a loss.

§ Statistically different at $p < 0.01$ from all patients.

TABLE 3. *Surgery: Non-CC-Stratified DRGs Cost by Hospital Service and CCs*

CC Category	Room and Board	Laboratory*	Blood	X-Ray	Operating Room/ Recovery Room	Central Supply/ Pharmacy	Other	Total
None	3837†	454†	17†	197†	1627	231†	516†	6225†
1 or 2	4807†	682†	25†	336†	1616	342‡	914†	8721†
3 or 4	6500	1023	33	483	1655	437	1,207	11,338
Over 4	15,637†	3076	94†	1248†	2224†	992†	3,885†	27,157†
All	6,287	1,040	34	461	1,717	425	1,302	11,271

* Urinalysis, hematology, coagulation, biochemistry, and microbiology.

† Statistically different at $p < 0.01$ from all patients.
‡ Statistically different at $p < 0.05$ from all patients.

ing DRG weight index constant) as the number of CCs per patient increased (the ratio was 226% greater for patients with over 4 CCs *vs.* patients with no CCs). Mean total hospital cost by hospital service demonstrated considerable variation among CC groups, but almost always increased as CCs per patient increased (Table 3). The largest component of total hospital cost was for room and board, followed by operating room/recovery room, other, laboratory, radiology, central supply/pharmacy, and blood.

The per cent of outliers rose as CCs per patient increased; patients with over four CCs had a 23% outlier rate (Fig. 1). The percent mortality rose as CCs per patient accumulated; patients with over 4 CCs had almost a 20% mortality rate (Fig. 2). Clinical resource utilization increased as CCs per patient rose for SICU utilization (Fig. 3), plasma products utilization (Fig. 4), blood utilization (Fig. 5), and emergency admission (Fig. 6). Linear regression analysis demonstrated an R^2 value of 0.10 ($p < 0.0001$) for total hospital cost (corrected for DRG weight index per patient) *versus* the number of CCs per patient.

Discussion

The purpose of this study was to analyze hospital resource consumption for Medicare surgical patients in the 147 non-CC–stratified surgical DRGs. Patients with a greater number of CCs per DRG had greater resource consumption than patients in these same DRGs with fewer CCs. Only about 50% of this greater resource consumption was explained by a higher DRG weight index. Thus, more CCs per patient per DRG generated greater total hospital cost, a longer hospital LOS, financial losses under DRG reimbursement, more procedures per patient, a greater proportion of outliers, and a higher mortality rate compared to patients in these same DRGs with fewer CCs per patient. These findings raise the question of the equity of DRG reimbursement vis-à-vis surgical patients in these non-CC–stratified surgical DRGs. This study suggests that patients in these DRGs with a greater number of CCs may be an *unattractive* population for hospitals.

At this time the Congress of the United States, the Health Care Financing Administration (HCFA) and the Prospective Payment Assessment Commission (ProPAC) are examining potential solutions to improve the equity of DRG hospital payment along the lines suggested in this study. Two ProPAC recommendations, for example, would further stratify some DRGs by CCs. Recommendation no. 21 contained in the April, 1987 report to the Secretary of Health and Human Services states, "DRGs should be defined on the basis of the

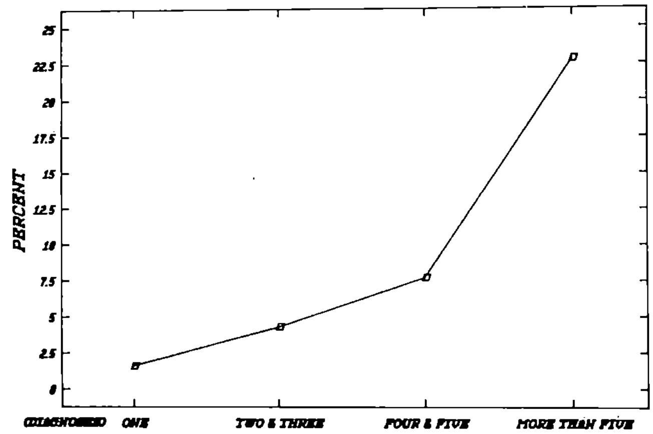

FIG. 1. The per cent of outliers rose as the number of diagnoses per patient accumulated.

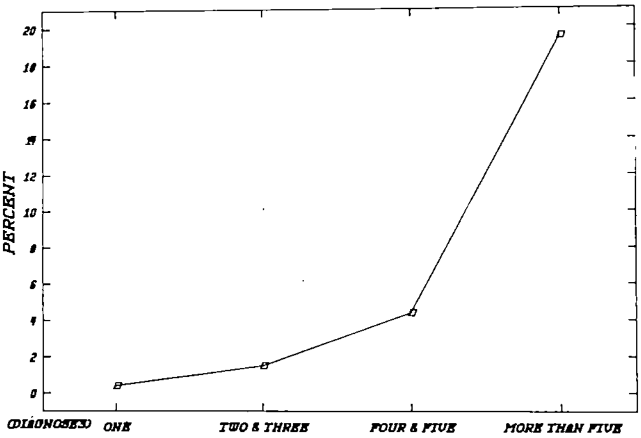

FIG. 2. Patients with over 5 diagnoses per patient had almost a 20% mortality rate.

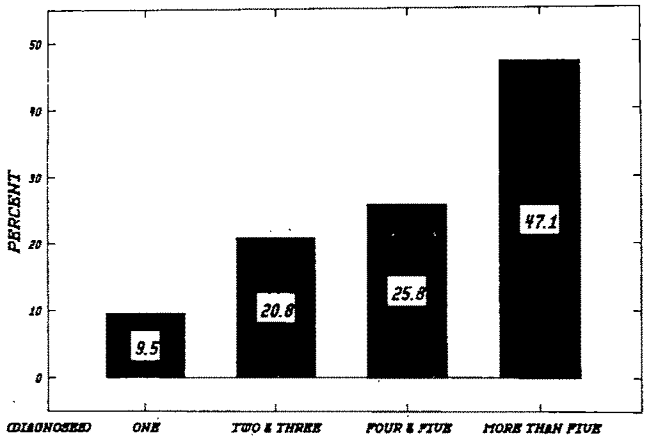

FIG. 3. SICU utilization rose with the number of diagnoses; almost half of patients with over 5 diagnoses were treated in the SICU.

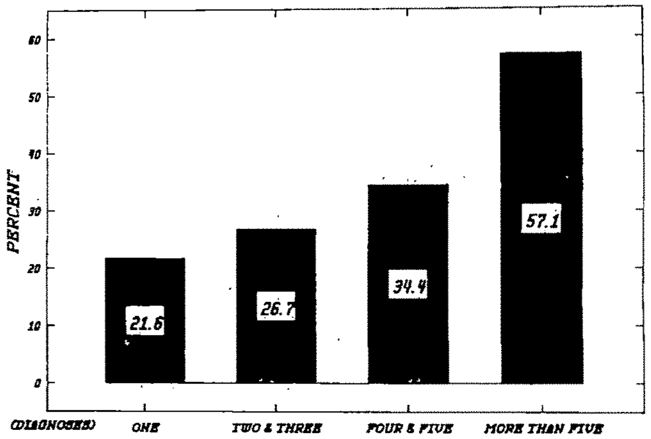

FIG. 5. More than 50% of patients with over 5 diagnoses required blood.

presence of a CC, regardless of age. . . . *The Secretary should determine whether other DRGs should also be split on CC.*"[6] Our study demonstrates that *other DRGs* (*i.e.*, many of the non-CC–stratified surgical DRGs) should be split by CC. In addition, ProPAC recommendation no. 22 in this same report states, "The Secretary should evaluate several possible approaches, *including DRG-specific CCs on the basis of resource intensity,* and the specification of levels of complexity among the CCs."[7] This ProPAC recommendation is also supported by our findings for the non-CC–stratified surgical DRGs. However, critics of these proposals contend that providing further incentives to modify DRGs by CCs will result in another round of *DRG creep,* namely, hospital incentives to find more CCs per medical record. Thus, it is unclear whether an additional modification of some surgical DRGs will be implemented along the lines of CC splits, or what form this modification might take.

Another possibility involves stratifying surgical DRGs for severity of illness (*i.e.*, the degree of each patient's illness).[8] There are a number of methods being studied by the federal government as potential DRG severity modifiers. Several of these require substantial additional data collection by hospitals that would require extra administrative costs. In addition, critics maintain that none of the systems are sufficiently mature or widely enough tested to be implemented for the 11 million annual Medicare acute hospitalizations at the 6000 U.S. hospitals. Thus, it appears likely that no DRG severity modifier will be implemented in the near future.

It appears that the practicing surgeon is being placed between diminishing hospital resources to treat patients and an increasing scrutiny of the quality of that surgical care.[9] This study demonstrates that resource dilemmas may become a significant problem for treating certain types of patients or for certain groups of hospitals regarding the non-CC–stratified surgical DRGs analyzed here. Although surgeons must be sensitive to the increasing problem of scarce resources in the care of surgical patients, we must also emphasize equitable hospital

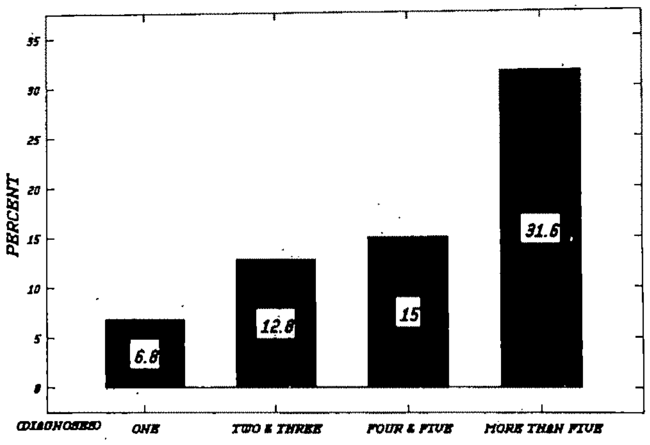

FIG. 4. Plasma product utilization was highest for patients with over 5 diagnoses.

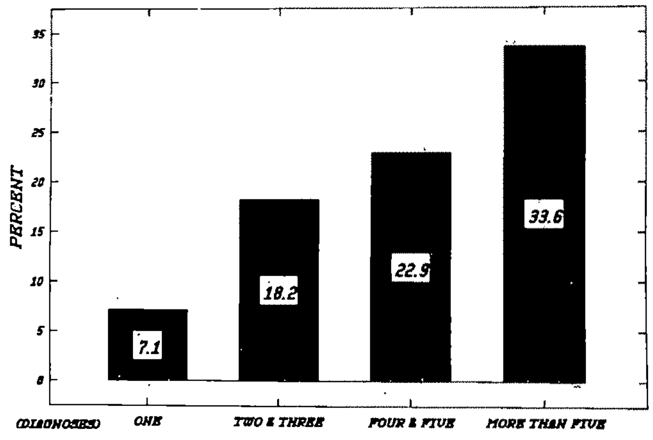

FIG. 6. Emergency admission rose with the number of diagnoses; one third of patients with over 5 diagnoses were emergencies.

payment for the treatment of surgical diseases. Surgeons must continue to analyze the equity and efficiency questions facing the field of surgery and advocate equitable high quality surgical care.

Conclusions

This study of 2647 surgical patients treated at an academic medical center analyzed the equity of the 147 non-CC–stratified surgical DRGs. Our data demonstrated that patients in these DRGs with more CCs per DRG had greater resource consumption, higher financial risk, and a poorer outcome than patients in these same DRGs with fewer CCs. This study thus suggests that the current DRG system is inequitable vis-à-vis groups of patients and types of hospitals treating patients in these non-CC–stratified surgical DRGs.

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Reoperations for Persistent and Recurrent Secondary Hyperparathyroidism

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Forty-nine reoperations for persistent or recurrent secondary hyperparathyroidism (HPT) in 30 patients are reported. The patients are part of a total of 184 patients operated on for secondary HPT; 28 reoperations in 18 patients were performed in the neck or in the upper mediastinum for remaining glands. Eleven reoperations at the forearm autograft revealed hyperplasia of the grafted tissue as the reason for recurrent disease in seven patients; they were treated by excision of all grossly enlarged particles. Ten patients received autologous cryopreserved tissue because of permanent postoperative hypoparathyroidism. The rate of graft-dependent recurrent HPT was 7%, and inadequate graft function was found in 6% of the patients.

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Experience in surgical treatment of secondary hyperparathyroidism (HPT) has been accumulated since 1960.[1] Today the treatment of choice is total parathyroidectomy and immediate autotransplantation of fresh parathyroid tissue into the forearm muscle; however, some authors prefer subtotal parathyroidectomy. There are a considerable number of reports on both procedures for secondary HPT.[2] Results on reoperations for this disease have only once been published.[3]

The reasons for reoperations based on the failure to find all hyperfunctioning tissue in the neck are comparable in primary and secondary HPT. This is not true for the continued postoperative stimulation of growth and function of parathyroid tissue in secondary HPT—in the neck or at the graft site—due to chronic renal failure. This stimulus can only be stopped by renal transplantation. Inadequate function of the grafted tissue is a further problem that deserves to be managed.

The indications for reoperations in secondary HPT are the same as for the first operation: normocalcemia combined with markedly elevated alkaline phosphatase and radiologic signs of renal osteopathy (stage II) or the hypercalcemic variant of secondary hyperparathyroidism (stage III of the classification proposed in Table 1).[4] Persistence of secondary HPT can be defined in the same way as in primary HPT, namely, as the persistence or recurrence of the typical symptoms, laboratory parameters, and radiologic signs within 6 months.[5] A later occurrence of symptoms and signs of secondary HPT should be classified as recurrence.

Patients and Methods

Between 1975 and February 1987, 184 patients were operated on for secondary HPT. Thirty of these had 49 reoperations for recurrent or persistent disease or for permanent postoperative hypoparathyroidism (Table 2). There were 17 males and 13 females with ages ranging from 17 to 55 years (median: 32 years). All were receiving chronic maintenance hemodialysis.

Reoperations in the Neck

In 18 patients a total of 28 reoperations in the neck were performed, one reoperation in 12 patients each, two in 3, three in 2, and four in 1 patient. Ten of these 28 reoperations were unsuccessful, four in our own institution. During the 18 initial operations and the 10 unsuccessful reoperations 45.5 glands were removed (Table 3).

The following 18 and up until the current final reoperations in the neck in these 18 patients form part of this report. The time interval between the first operation and the last procedure was between 4 weeks and 19 years (median: 28 months). The indication for these reoperations was stage II disease in five patients, 4 months to 9

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TABLE 1. *Classification of Secondary HPT Related to Indication for Surgery*

	Stage I	Stage II	Stage III
Serum-calcium (mmol/L)	<2.6	<2.6	>2.6
Alkaline phosphatase (U/L)	<300	>300	Normal or elevated
Finger x-ray	Normal	Subperiosteal resorption, acro-osteolysis	Subperiosteal resorption present or not
Indication for surgery	None	Relative, depending upon severity of fibro-osteoclasia	Absolute

years after the first procedure and in the other 13 patients stage III of secondary HPT according to the classification given in Table 1. In five of these 18 patients a recurrence of the disease was noted 29 months to 9 years after the first procedure. In the other 13 patients persistent secondary HPT was present. Some of the patients were investigated by sonography, CT scan, MRI, and thallium-technetium-subtraction scan for preoperative localization. The procedures were helpful only in the minority of the patients. We therefore restrict the use of these procedures even before reoperations, relying more on the surgical anatomy of the parathyroid glands.

In the 18 final reoperations another 31.5 parathyroid glands were removed (Table 4). Added to the 45.5 glands previously removed, this gives a total of 77 glands in 18 patients, which means an average of 4.3 glands were removed per patient. In ten of the 18 patients the glands were found in the mediastinum, in nine of these in the thymus. Five of the glands removed must be considered as supernumerary fifth glands. They were all excised by cervical thymectomy. The other glands were found in the neck.

In two of these patients the capsule of a parathyroid gland had been inadvertently opened and parathyroid cells were spilled in the operative field. Though macroscopically this material was removed completely, dispersed cells obviously grew in the neck, causing recurrent disease. One of these patients needed three reoperations finally removing all fat and connective tissue at this side of the neck until he was completely cured. Histology showed multiple distributed islets of hyperplastic parathyroid tissue in the specimen.

In 16 of the 18 patients calcium levels have remained normal after their last operation. Normal calcium levels have been established by a number of procedures. In six patients fresh parathyroid tissue was autografted in a forearm muscle since during all procedures a minimum of four parathyroids was excised, proved by histology. Four patients had no parathyroid function after the final operation and received a deferred autograft of cryopreserved tissue. Three other patients have normal serum calcium levels without autografted tissue after removal of two, three, and five glands, respectively. One patient was normocalcemic after removal of the fifth gland, with a normal functioning autograft, which was performed earlier. The same is true for the two patients where parathyroid cells had been inadvertently distributed in the operative field. One patient displays continuous hypercalcemia despite the resection of four glands in the neck and the removal of the autografted tissue in the forearm. One patient is hypocalcemic after removal of four glands. He will be autografted in the near future.

As complications of all reoperative procedures in the neck, one permanent and one transient recurrent nerve palsy was noted. There was no other postoperative morbidity nor mortality.

Graft Excision at the Forearm

In nine patients 11 procedures at the forearm graft were performed. All patients were preoperatively classified as having recurrent disease 32 to 80 months after autotransplantation of fresh tissue (median: 42 months). Hyperfunction after replantation of cryopreserved tissue

TABLE 2. *Number of Type of 49 Reoperations Performed in 30 Patients*

Reoperations in the neck	Excision of Graft	Regrafting	Total No. of Reoperations	Patients
21	—	—	21	11
3	3*	—	6	3
4	—	4	8	4
—	8	—	8	6
—	—	6	6	6
Total 28	11	10	49	30

* In one case the area was explored without finding any parathyroid tissue.

TABLE 3. *Number of Parathyroid Glands Removed in 18 Initial and 10 Previous Reoperations in 18 Patients*

Patients	Glands
1	0
2	1
7	2
2	3
1	3.5
5	4
Total 18	45.5

TABLE 4. *Number of Parathyroid Glands Removed During the 18 Up to Now Final Reoperations in 18 Patients*

Patients	Glands
1	0
8	1*
5	2
2	3
2	4
Total 18	31.5

* This was the half gland mentioned in Table 3.

was not noted up to now. The indication for resection of the graft was in seven patients stage III, in two stage II of secondary HPT (Table 1) with recurrence of symptoms and signs of renal osteopathy. In eight patients hyperplastic tissue in the forearm was palpable as solitary or multiple nodules, which it could be visualized by sonography (Fig. 1). Additionally, in four patients a thallium scan was performed, which also displayed the autografted hyperplastic tissue (Fig. 2). In one patient there was no tissue palpable nor demonstrable by the imaging procedures.

The diagnosis of recurrent graft dependent HPT by determination of parathyroid hormone in the blood taken from the antecubital vein of the grafted *versus* the contralateral arm was not successful despite the fact that a highly sensitive midregional assay was used and blood was taken 1, 3, and 5 minutes after applying a tourniquet. Only two of the nine patients had a gradient of the grafted *versus* the contralateral side of 2 to 1 and 5 to 1, respectively. It should be noted that parathyroid hormone levels even at the contralateral side were 25 to 30 times normal. In the other seven patients without a demonstrable gradient, background levels of parathyroid hormones were between 3 and 80 times normal (mean: 38 times normal). In two of the nine patients postoperatively the hypercalcemia was not considered as graft-dependent. One of them remained hypercalcemic after excision of parathyroid tissue at the graft site. Later evaluation showed hyperfunctioning tissue in the neck. In the second patient the graft site was explored without finding any parathyroid tissue. He remained hypercalcemic until spilled hyperplastic parathyroid tissue in the neck was resected. These two patients belong to the aforementioned group of 18 patients reexplored in the neck.

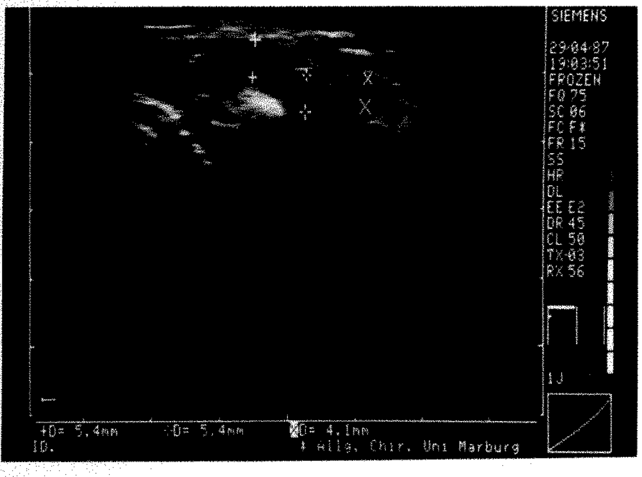

FIG. 1. Three particles of hyperplastic parathyroid tissue autografted in the forearm demonstrated by sonography.

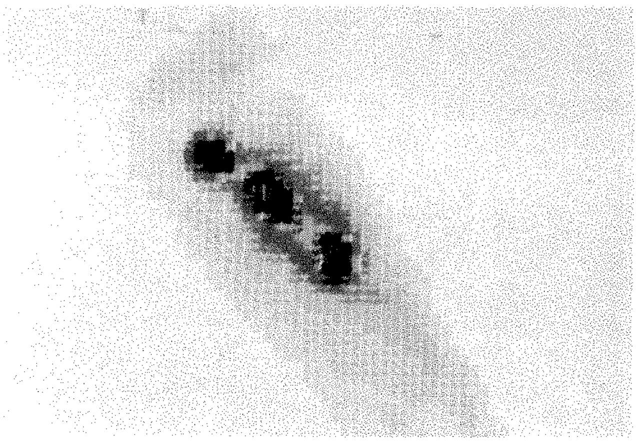

FIG. 2. Thallium scan of a hyperplastic autograft in recurrent renal HPT. Three hyperplastic particles are demonstrated.

During the resection of the grafted tissue, which was performed under local anesthesia on an outpatient basis, all palpable parathyroid nodules were removed, up to six nodules per patient. All hyperplastic nodules were surrounded by a capsule of connective tissue. An infiltrating growth in the surrounded muscle tissue was not observed. The nonpalpable part of the graft was left behind.

In seven patients serum calcium levels were normal after resection of the hyperplastic tissue in the arm. The follow-up ranged between 7 and 73 (median: 22) months. Only one patient is still hypercalcemic. The autograft is neither palpable nor detectable by sonography. Therefore, we conclude that HPT is caused by residual parathyroid tissue in the neck despite the removal of four glands.

The seven patients with graft-dependent recurrent HPT belong to a group of 117 patients who have been continuously followed in our department with a minimum follow-up of 1 year; 101 of these were autografted into the forearm. In the other patients subtotal parathyroidectomy was performed as part of a controlled trial that will be published later. The percentage of graft-dependent recurrent HPT in our material is, according to these figures, 7% (7 out of 101 patients). Histology of all tissue removed from the graft site revealed hyperplasia. In no case were signs of malignancy demonstrated.

Replantation of Autologous Cryopreserved Tissue

In 10 patients cryopreserved autologous tissue was grafted in a forearm muscle. The indication in four patients was aparathyroidism after reoperation in the neck without prior autotransplantation of fresh material and in six patients a nonadequate function of previously grafted fresh tissue after total parathyroidectomy requiring high dose treatment with calcium and vitamin D metabolites. The percentage of inadequate function of autografted fresh parathyroid tissue is therefore 6% (6 out of 101 patients).

The parathyroid tissue in the four patients without a fresh autograft was cryopreserved between 2 and 10 months, in the other patients between 2 and 42 months until reimplantation. In the first of these 10 patients 20 particles of 1 mm^3 were regrafted in the forearm muscle; 20% of the tissue was necrotic as demonstrated later. Sufficient graft function was noted after 21 months. In the other nine patients the percentage of necrotic tissue after freezing, cryopreservation, and thawing was examined prior to replantation by a previously published method.[6] It was between 1.7% and 50% (median: 20%). By compensating the necrosis rate using more than 20 particles depending on the degree of necrosis, the grafts functioned normally 3 to 7 months after replantation in eight patients. One patient in whom 50% of the tissue was necrotic received 40 particles. She discontinued her supplemental treatment several weeks thereafter, displaying low serum calcium levels. After 10 months she was normocalcemic.

Discussion

Our results show that most reoperations for secondary HPT must be performed because of hyperfunction of residual tissue in the neck or in the mediastinum. This corresponds with the experience of Dubost et al.[3] Since during reoperations most parathyroid glands were found at a normal site, an inadequate initial exploration (removal of less than four glands) must be assumed. It should be emphasized that in ten of the 18 patients the residual tissue was found in the mediastinum, mostly within the thymus, in five of these patients as a fifth gland after four glands had been removed previously. The removal of four parathyroid glands is therefore not equivalent to a sufficient parathyroidectomy in all patients.

According to Wang, 5–6% of all patients have supernumerary glands that are almost always found in the thymus.[7] In patients with secondary HPT these glands may be smaller than the other four and may secrete only a smaller amount of parathyroid hormone compared to the glands removed. Postoperatively due to the continuous stimulation of growth caused by renal failure, they can increase in size and cause recurrence.

We hope to reduce the number of reoperations if this experience can be part of a standardized initial operation. Together with the neck exploration and the removal of four glands that are usually found there, at least both thymic tongues or the whole thymus on both sides should be resected. This is also recommended by Diethelm.[8] This thymectomy should always be performed if one or both lower glands are not found in the neck.

Care should also be taken not to open the parathyroid capsule during exploration because this can lead to an inadvertently performed autotransplantation including a possible later recurrence of secondary HPT. Fresh parathyroid tissue should only be autografted in primary procedures or in reoperations if at least four histologically proven parathyroid glands and the thymic tongues have been removed. If not, autotransplantation should be cancelled and the tissue must be cryopreserved for possible deferred autografting.

Hyperfunction of the autograft in the forearm was the second most common reason for reoperations. All graft-dependent recurrences occurred after autotransplantation of fresh tissue and led to symptomatic disease and reoperation after a minimum of 32 months. In an individual patient with persistence or recurrence of secondary HPT after total parathyroidectomy and autotransplantation it is difficult to localize the source of hormone excess, namely, to differentiate whether it is in the neck or at the forearm. In our experience, simple procedures like palpation, sonography, and in some cases thallium scan can be helpful. They display enlarged parathyroid tissue within the muscle tissue. The parathyroid hormone determination in the blood, draining the graft bearing arm *versus* the contralateral arm, was not successful. One possible reason for this failure is the high level of parathyroid hormone in the systemic blood that can disguise a hormone gradient. The determinations in patients with a normal graft function show better results in the presence of generally lower systemic levels than were found in our patients.[9,10]

It is surprising that only a maximum of 6 of 20 autografted particles were enlarged. We also discovered parathyroid tissue particles of normal size during exploration of the graft site. We therefore do not agree with Dubost et al.,[2] who recommend the excision of the whole autograft. We excise only the palpable or visible hyperplastic nodules since this procedure led to a normal serum calcium in the majority of our patients. Permanent postoperative hypoparathyroidism is a severe complication after parathyroid surgery. It can be avoided by a permanent medication with calcium and vitamin D metabolites or by autotransplantation of cryopreserved tissue.

The operative alternative avoids the medication, which is sometimes difficult to manage. If the autografted tissue functions, it allows a normal calcium and phosphate metabolism and remineralization of bone.[11] Since permanent postoperative hypoparathyroidism can occur after total parathyroidectomy or after reoperations for recurrent or persistent HPT, cryopreservation should be performed after all these operations even if the majority of the patients will not need the cryopreserved tissue later. In our experience all patients regrafted by autologous cryopreserved tissue had a normal graft function after compensation of the necrosis rate of the cryopreserved tissue by grafting a larger amount of tissue.[6,11] A simple method for cryopreservation developed by us can lead to a wider use of this method in parathyroid surgery.[11]

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The Limitations of Diagnosis of Carotid Occlusion by Doppler Ultrasound

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Duplex scanning has been advocated as an acceptable alternative to angiography in the preoperative evaluation of carotid artery stenosis. To evaluate the accuracy of carotid Doppler in differentiating severe carotid stenosis from occlusion, we compared the results of angiography with duplex scanning in 124 carotid arteries (62 patients) and with continuous-wave Doppler in 662 carotid arteries (331 patients). The specificity was 95–99%, sensitivity was 86–96%, and accuracy was 95–98%. Duplex scanning wrongly identified occlusion in four arteries and failed to detect occlusion in one artery. In making decisions prior to carotid endarterectomy, even infrequent errors are unacceptable. We recommend angiography of all surgical candidates with apparent severe stenosis when the internal carotid artery cannot be clearly identified on duplex, or to distinguish apparent occlusion from undetectably low blood flow.

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DISTINGUISHING BETWEEN severe carotid stenosis and occlusion is critical since it determines the prognosis and management of the patient. Carotid endarterectomy is a well-established and widely accepted therapy in patients with symptomatic carotid stenosis, but it is rarely worthwhile to attempt reconstructive surgery on occluded arteries.[1] Angiography, the *gold standard* for evaluating carotid disease, is the only way at present to distinguish this difference. An accurate, noninvasive diagnostic method is needed to avoid the hazards of angiography.[2,3] Some authors suggest that carotid Doppler can substitute for angiography in selected patients.[4–6]

Doppler sonography and digital subtraction angiography have become accepted methods of evaluating extracranial carotid disease.[7–13] Digital subtraction angiography involves the hazards of injected contrast media,[14] while ultrasound methods are without risk. We compared continuous-wave and duplex scanning with conventional and digital subtraction angiography to assess the accuracy of these techniques in detecting occlusion of the internal carotid artery and to determine whether duplex scanning is superior to continuous-wave Doppler.

Materials and Methods

Over an 18-month period (January 1, 1985 to June 30, 1986) all consecutive patients found to have one occluded carotid artery on Doppler scanning and who were referred for cerebral angiography, were analyzed retrospectively. Continuous-wave Doppler (Carolina Medical Electronics Dopscan Plus 1060 [Carolina Medical Electronics, King, NC], with spectral analysis and periorbital directional Doppler, with B-mode imaging and single-gate pulsed Doppler) was compared with angiography in an additional 331 patients. Ultrasonographic examinations were performed by two experienced technicians, with the patient lying supine and a 5-MHz probe applied to the extended neck at a 60-degree angle to the sagittal plane. Tape-recorded studies were interpreted by one of the study physicians without knowledge of the angiographic findings.

The ultrasonographic criteria for occlusion were a combination of: (1) failure to detect a flow signal from the internal carotid artery with continuous-wave Doppler; (2) asonic artery on pulsed-wave Doppler associated with plaque seen with B-mode imaging and longitudinal pulsation of the artery walls; and (3) reversed flow in the ophthalmic, frontal, or supraorbital arteries.

Carotid biplanar angiograms were interpreted by neuroradiologists who had no knowledge of the results of the sonographic evaluation.

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TABLE 1. *Accuracy of Duplex Scanning Compared with Angiography in Detecting Carotid Occlusion in 124 Arteries**

Duplex Scanning	Angiography		
	Occlusion	Nonocclusion	Total
Occlusion	24	4	28
Nonocclusion	1	95	96
Total	25	99	124

* Sensitivity = 96%, specificity = 95%, postive predictive value = 86%, negative predictive value = 99%.

Results

Sixty-two consecutive patients with one occluded artery demonstrated by duplex scanning (50 men and 12 women, mean age 69 years) had either digital-subtraction or conventional angiography. Both duplex scanning and angiography detected occlusion of 24 arteries, but duplex scanning wrongly identified occlusion in four arteries (false-positive) and failed to detect occlusion in one artery (false-negative), resulting in a sensitivity of 96%, specificity of 95% and accuracy of 95% (Table 1).

When continuous-wave Doppler results in 331 patients (662 arteries) were compared with angiography, Doppler incorrectly diagnosed occlusion in seven arteries and failed to detect occlusion in another seven arteries. The sensitivity was 86%, specificity 99%, and accuracy 98% (Table 2).

Discussion

The reported accuracy of duplex ultrasound in predicting the degree of stenosis varies from 80–97%,[9,11,15–17] but no study yet has specifically evaluated its diagnostic accuracy in carotid occlusion. Too few occluded arteries were identified in published studies to warrant separate statistical analysis.[11,15–24] Levien et al.[25] evaluated a variety of noninvasive tests (including continuous-wave but not duplex ultrasound) in the diagnosis of carotid occlusion and found a sensitivity of 70% and specificity of 98%. Pooling all available data[11,15–24] on duplex scanning over the last five years, results are very similar to ours (Table 3).

The low frequency of missed diagnoses in our study (2–5%) indicates that continuous-wave and duplex ultrasound are both relatively reliable in detecting occlusion, but even infrequent false-negative results are disturbing, since such patients may undergo unnecessary surgery. More significantly, severe stenosis (95–99%) was found at angiography in four patients who had apparent carotid occlusion on duplex scanning. If these patients were assessed only by Doppler, they would remain unoperated and at high risk of stroke.

TABLE 2. *Accuracy of Continuous-wave Scanning Compared with Angiography in Detecting Carotid Occlusion in 662 Carotid Arteries**

Continuous-wave Scanning	Angiography		
	Occlusion	Nonocclusion	Total
Occlusion	42	7	49
Nonocclusion	7	606	613
Total	49	613	662

* Sensitivity = 86%, specificity = 99%, positive predictive value = 86%, negative predictive value = 99%.

TABLE 3. *Analysis of Pooled Data*[11,15–24] *Comparing Duplex Scanning with Angiography in Detecting Carotid Occlusion in 2095 Arteries**

Duplex Scanning	Angiography		
	Occlusion	Nonocclusion	Total
Occlusion	211	26	237
Nonocclusion	37	1821	1858
Total	248	1847	2095

* Sensitivity = 85%, specificity = 98%, positive predictive value = 89%, negative predictive value = 99%.

In two cases of apparent occlusion on duplex scanning, the external carotid artery was superimposed on the internal carotid artery so they could not be differentiated. A falsely positive temporal *tapping test*[26] occurred in another case when the vibrations were transmitted down the external and up the internal carotid artery. In a fourth case, the angiogram revealed a vascular anomaly, with a common origin of the right innominate and left carotid arteries so duplex scanning could not image the left carotid system. In three of these cases of apparent occlusion the artery was asonic but periorbital flow was normal. Of the seven instances of false-positive diagnoses on continuous-wave scanning, four were due to severe stenosis, where blood flow was so reduced as to be undetectable, and in one case extensive calcification masked severe stenosis.

Ultrasound evaluation, without angiographic confirmation, has been advocated as the basis for carotid surgery for some patients.[4–6] This is probably acceptable for patients with tight stenosis when the internal carotid artery is clearly identified on duplex imaging. When appearances suggest occlusion, angiography is needed to determine whether blood flow is so reduced as to be undetectable by Doppler or truly absent.

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The Improving Long-term Outlook for Patients over 70 Years of Age with Abdominal Aortic Aneurysms

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During the past decade, selective criteria for elective surgery for abdominal aortic aneurysms have been refined based on natural history and aneurysm expansion information. Using these criteria, contemporary preoperative preparation and newer intraoperative technical adjuncts, 123 consecutive patients underwent elective resection with 1 death (mortality rate: 0.8%). These include all patients operated on with both elective and urgent aneurysms at this institution since 1978, with the exception of those with frank rupture. Most importantly, however, the 5-year life-table survival of all of these patients (average age: 71.3 years, range 46–96 yr) was 72%, including both hospital and late mortality rates. More than half of the patients were over 70 years old (78 cases), with no hospital deaths and a 5-year life-table survival probability of 67%. For those under 70 years of age at the time of operation, the 5-year life-table probability of survival was 79%. We believe that these accomplishments were a direct result of an aggressive policy of screening for and selectively treating coronary disease and carotid stenosis preoperatively and the utilization of such intraoperative adjuncts as routine Swan-Ganz monitoring, autologous blood transfusion, the cell saver, and the frequent use of the tube grafting (50%). Thus, with proper selection, the outlook for the patient over 70 years old with an elective abdominal aortic aneurysm resection now approaches that of the normal population (67% *vs.* 69%).

REFINED DIAGNOSTIC TECHNIQUES for infrarenal abdominal aortic aneurysms have made it possible to identify patients at risk from this condition at an earlier stage, and permit a more careful evaluation of aneurysm size and associated risk factors.[1,2] Long-term follow-up of unoperated patients with small abdominal aortic aneurysms by ultrasound, and more recently by CT scanning, has determined the mean expansion rate for aneurysms under 6 cm in size to be 4 mm/yr.[2] Thus, surgical selection has improved parallel to advancing surgical management techniques for such patients. As a result, the mortality rate associated with elective surgery for abdominal aortic aneurysms has decreased significantly each of the last several decades.[3–7] More important, however, has been the effect of improvement in diagnosis, selection, and management on the longevity of patients with this condition.

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The opening of the Green Hospital of Scripps Clinic in 1978 permitted the acquisition of data regarding all patients operated on in this center by two surgeons (E.F.B. and R.B.D.) with a single protocol since the inception of surgical activity. This report summarizes our initial experience with elective surgery for abdominal aortic aneurysm at the Scripps Clinic.

Materials and Methods

One-hundred twenty-three consecutive patients were subjected to elective surgery for abdominal aortic aneurysms from January 1, 1978 through December 1985. Their charts were surveyed for data regarding aneurysm size, general physical condition, presence of associated risk factors, and prior cardiovascular surgery. In addition, the preoperative angiograms were reviewed for documentation of additional para-aneurysmal disease, and particularly for unusual renal arterial anatomy, renal artery stenoses, and anomalies. Operative reports were abstracted to obtain data regarding aneurysm size, anesthetic time, operative time, aortic cross-clamp time, type of graft implanted, utilization of the cell saver, and operative blood loss. Information was also obtained regarding operative mortality and hospital morbidity rates, and all data were categorized by patient age. All surviving patients were contacted to determine their current health status, and an effort was made to deter-

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mine the time and cause of death of all patients who died. Such information was obtained by review of the patients' charts, contacting the Bureau of Vital Statistics of San Diego County, and direct written or verbal contact with the patient, the family or personal physician. Every effort was made to confirm the final cause of death from autopsy or death certificate information.

All data were entered on a VAX 11/750 computer using CLINFO software for clinical research management analysis. Life-table analyses were performed according to the procedure of Kaplan and Meier[8] and Gehan.[9]

Selection for Surgery

General criteria for operative intervention included all aneurysms of 5 cm or more in largest transverse diameter in good risk patients. Noninvasive tests were routinely used to confirm the diagnosis and to estimate aneurysm size. During the earlier years of the study, ultrasound was the predominant method of noninvasive examination, but more recently CT scanning has been used liberally and is now considered the diagnostic technique of choice. All patients with symptomatic aneurysms were operated on, regardless of patient's age or aneurysm size. Included in these data are all patients with urgent procedures in whom the aneurysm was discovered to be intact at the time of surgery.

Questionable operative indications. Contraindications to surgery included a myocardial infarction within 3 months, the presence of intractable congestive heart failure, dyspnea at rest, permanent significant residual neurologic deficit from stroke, or advanced renal disease with a creatinine of 3 or greater. In addition, the presence of other terminal diseases with a life expectancy of less than 3 years was considered a contraindication to elective surgery. Poor risk patients with small asymptomatic abdominal aneurysms (less than 6 cm) were followed routinely at 3-month intervals with echography or CT scanning and were operated upon if they became symptomatic or if the aneurysm reached a size of 6 cm. In addition, the rapid enlargement of an aneurysm (greater than 1 cm in a year or less) in a poor risk patient was considered an indication for surgery.

Preoperative routine. All elective aneurysm patients were subjected to treadmill coronary stress testing and cardiologic consultation. A positive stress test was an indication for coronary angiography, and angiographic evidence of severe coronary disease such as greater than 90% stenosis of the left main, right main, or left anterior descending coronary arteries, even if asymptomatic, was considered an indication for preliminary coronary bypass. In addition, a noninvasive carotid duplex scan was performed on any patient in whom there was a history of a cerebrovascular event or evidence of a carotid bruit. Stenoses greater than 80% by diameter were treated by staged carotid endarterectomy. During the past year, patients were informed about and encouraged to participate in an autologous blood donation program in which 1 or 2 units of blood were donated during the 2 weeks prior to admission for aneurysmectomy. A minimum period of 6 days was required between the last blood donation and admission for elective surgery.

On the day of admission all patients were subjected to formal contrast aortography to define the status of their renal and visceral vessels, the proximal extent of aneurysms suspicious for suprarenal involvement, and the extent of distal iliac disease. A Swan-Ganz catheter was placed and the patient transferred to the intensive care unit for hydration and cardiac monitoring the evening before surgery.

Current operative routine. All patients were monitored with both an intra-arterial line and the Swan-Ganz catheter. Cefazolin was administered to all patients preoperatively. In addition, more recently intrathecal morphine was injected just after anesthetic induction to minimize postoperative pain. The abdominal wall was prepared with Betadine and covered with a Vi-drape. All patients were operated on through a vertical midline transperitoneal incision. The Gomez self-retaining retractor greatly facilitated exposure of the aneurysm and virtually eliminated the need for a second assistant. Proximal dissection was minimized and limited to the area of the neck of the aneurysm. Further dissection usually was limited to the common iliac vessels. The patient was systemically administered heparin 5000 U I.V. Occlusion of the common iliac arteries was generally performed first to prevent atheromatous embolization, followed by proximal aortic clamping with Wylie hypogastric artery clamps, which offer little interference to the operating surgeon. Preclotted knitted Dacron prostheses were used routinely. The Hemonetics Cell Saver (Haemonetics Corp., Braintree, MA) was utilized during the last 3 years on all elective cases. Tube grafts were placed for reconstruction whenever possible. Prolene was used for all vascular anastomoses. Following coverage of the Dacron graft by a retroperitoneal closure in two layers, the area of dissection and graft implantation was irrigated with a Kanamycin and Bacitracin solution.

Details of the special operative techniques required to deal with simultaneous suprarenal extension, hypogastric aneurysms, horseshoe kidney, accessory renal arteries, renal stenosis, mesenteric vascular insufficiency, inflammatory aneurysms, and other complications are beyond the scope of this article, but we have followed conventionally accepted approaches to these situations.

Postoperative routine care included 3 to 4 days in the intensive care unit. Fiberoptic bronchoscopy was used

TABLE 1. *Preoperative Risk Facors*

Smoker	82.9
Hypertension	45.1
Prior myocardial infarction	19.7
Prior stroke	4.9
Diabetes	8.1
Respiratory insufficiency ($FEV_1 < 2$)	20.5
Renal insufficiency ($Cr > 1.5$)	12.2

Values are given as percentages.

liberally for atelectasis or retained bronchial secretions. The Swan-Ganz catheter and arterial line were generally removed on the first or second postoperative day as was the Foley catheter. The nasogastric tube was retained until full evidence of intestinal function was present. Prolonged nasal oxygen was monitored by room air blood gas analyses and usually used for 5 to 6 days. Prolonged hospital stays averaging 10 days were routine. Following discharge, all patients were entered in the Vascular Registry, and follow-up was requested at 1, 3, 6, and 12 months and then on an annual basis.

Patient Demographic and Risk Factors

One-hundred twenty-three patients were operated on during the review period; 102 (82.9%) were males and the mean age was 71.4 years (range; 46–93 yr); 102 of the patients were smokers (82.9%).

Pertinent risk factors are summarized in Table 1, and include hypertension in 54.9% and severe respiratory, cardiac, and/or renal disease in 18–21%. Seven patients (5.7%) had been subjected to prior coronary artery bypass; 6 (4.9%) had a previous history of stroke; and 5 had prior carotid endarterectomy (4.1%). Conditions requiring additional or modified surgery included inflammatory aneurysm (1), severe renal artery stenosis causing hypertension (1), horseshoe kidney (2), and inferior mesenteric artery reimplantation (1). None of the aneurysms extended above the renal arteries, requiring suprarenal resection.

Operative Factors

Mean aneurysm size at the time of surgery was 5.8 cm (range; 3–11). Anesthetic time averaged 3.5 hours (range: 2–6.3) and mean operative time was 2.4 hours (range: 1–5). Aortic cross-clamp time averaged 48 minutes. Tube grafts were employed in 50% of the patients and bifurcation grafts in the remainder. There was no difference in the mean aneurysm size between those in whom bifurcation grafts were necessary or where tube grafts could be used (Table 2). However, cross-clamp time was decreased from 52 to 40 minutes when tube grafts were inserted ($p < 0.001$). In addition, mean operating time was decreased from 2.5 to 2.2 hours.

TABLE 2. *Abdominal Aortic Aneurysm: Graft Type*

	Graft Type	
	Bifurcation	Tube
Aneurysm size (cm)	5.7 ± 1.3	5.9 ± 1.4
Cross-clamp time (min)	52	40 ($p < 0.001$)
Operating time (h)	2.5	2.2
Blood loss (mL)	1202	1288
N	61	61

TABLE 3. *Abdominal Aortic Aneurysm: Operative Morbidity Rates*

System	N
Cardiac	1
Pulmonary	4
Renal-GU	5
Peripheral vascular	3
DVT-PE	4
Gastrointestinal	2
Wound (superficial infections)	2
Sepsis (septicemia)	1
Retroperitoneal hematoma	1

Cell saver. Seventy-five patients were operated on prior to the initiation of routine cell saver use with an average blood loss of 1582 mL, and an average replacement of 4.1 U of bank blood. Since institution of the use of the cell saver on a routine basis, 47 additional patients have been operated on with a mean blood loss of 1087 mL and an average return of 3.2 U of cell saver blood (560 mL), which decreased the requirement for bank blood from 4.1 to 2.0 U.

Operative mortality and morbidity rates. There was one operative death within the hospital or 30-day postoperative course in the 123 consecutive patients in this series (0.8%). Operative morbidity rate is summarized in Table 3 and indicates a predominance of pulmonary, renal, peripheral vascular, and thromboembolic problems. Only one cardiac complication occurred (myocardial infarction), and there were no associated strokes. An analysis of morbidity rates by age group indicated only a modest increase after the age of 65.

Survival. The overall life-table probability of survival for all patients in this series at 5 years was 72%, including the operative mortality. For those patients who were hypertensive it was 73%. Patients with a prior history of myocardial infarction had a significantly reduced probability of 5-year survival at 51%, in contrast to those with a prior coronary artery bypass procedure who had a 100% likelihood of 5-year survival.

For the fifty-six patients less than 70 years of age the probability of surviving 5 years was 79%. For those between 70 and 79 years of age (N = 47) the probability of surviving 5 years was 67% and for those patients 80 years or older (N = 20) the probability was 66%. The comparative 5-year survival probability between those over and under 70 years of age is documented in Figure 1 and Table 4, and shows essentially no difference for

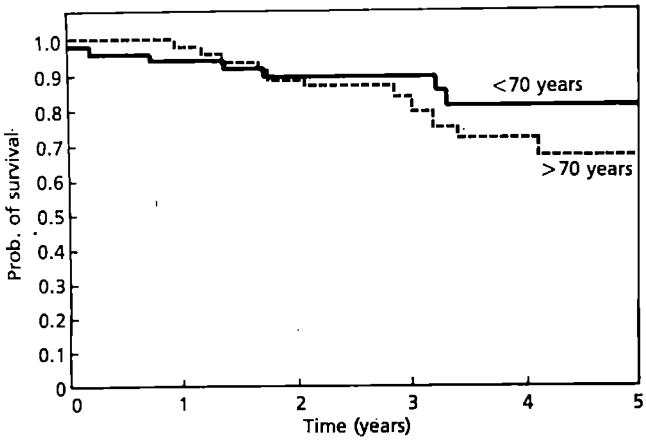

FIG. 1. Life-table analysis of survival following elective abdominal aortic aneurysm surgery.

the first 3 years and no significant difference at 5 years. Table 5 compares the current series with the recently published data of Crawford et al.[5] and of Hollier et al.[10] In all of these studies, the elective operative mortality rate for aneurysm surgery is in the range of 2% or less, and the likelihood of surviving 5 years following surgery is approaching that of the general population, which is 80% for an age- and sex-adjusted group. Most significant, however, is the increase in survival for the patient group over the age of 70. The report by Crawford et al.,[5] which includes Crawford's entire 25-year experience, includes patients treated in a much earlier era, with a 43% probability of 5-year survival for patients over 70, which must be regarded as representative of very good results during the time span reported. This impression is also confirmed by the data of Johnson et al.,[7] which includes the time span since 1952. However, the recent Mayo Clinic publications,[3,4,10] as well as our own, indicate a substantial increase in the likelihood of survival for those patients over 70, which closely approaches the survival of the general population with a similar age and sex distribution.

TABLE 5. *Abdominal Aortic aneurysm: Life Expectancy after Resection*

Author	Crawford (Baylor)	Hollier (Mayo)	Scripps Clinic
Year	1981	1984	1986
No. of patients	920	1112	123
Operative mortality rate (%)	1.9	2.6	0.8
5-year life expectancy (%)*	63	68	72
Age			
<60 yr	71	76	79
60–70 yr	66	71	
>70 yr	43	60	66

* General population (age- and sex-adjusted) = 80%.

Discussion

Improvement in the care of patients with abdominal aortic aneurysms during the 35 years since the first replacement procedures were introduced has been based on progress in the following areas:

1. *Early diagnosis.* Increased suspicion, and the ready availability of relatively inexpensive and extremely accurate noninvasive methods have permitted diagnosis at an earlier stage since the introduction of ultrasound in 1970 and CT scanning in 1980.[1,2] Both modalities are essentially 100% sensitive in the detection and accurate diagnosis of the disease, and are within 2–3 mm of operative size estimates. Thus, 80% of the aneurysms detected in the extensive UCSD series[2] during the past 15 years were 6 cm or less. Therefore, the clinician

TABLE 4. *Life-table Analysis of Survival Following Abdominal Aortic Aneurysm Surgery*

Months Postsurgery	No. of Patients Entering	Number Withdrawn	Number at Risk	Number of Deaths	Proportion Surviving	Cumulative Proportion Surviving
Patients under 70 years of age (N = 60)						
0–12	60	11	49	2	0.956	0.956
13–24	47	10	37	2	0.946	0.907
25–36	35	11	24	0	1.0	0.907
37–48	24	5	19	2	0.89474	0.812
49–60	17	9	8	0	1.0	0.812
61–72	8	1	7	0	1.0	0.812
73–84	7	4	3	0	1.0	0.812
85–96	3	3	0	0	—	—
Patients over 70 years of age (N = 63)						
0–12	63	16	47	0	1.0	1.0
13–24	47	2	45	5	0.889	0.889
25–36	40	15	25	2	0.92	0.818
37–48	23	5	18	3	0.833	0.681
49–60	15	4	11	1	0.909	0.620
61–72	10	7	3	0	1.0	0.620
73–84	3	2	1	0	1.0	0.620
85–96	1	1	0	0	—	—

is more frequently faced with a patient with a smaller asymptomatic aneurysm.

2. *Thorough cardiovascular evaluation.* Routine cardiac stress testing and frequent or routine cerebrovascular scanning has markedly reduced the incidence of cardiac and neurologic complications, which used to be most feared in elective aneurysm surgery. The identification of severe coronary or carotid arterial disease has become an indication for prior revascularization of these vessels. However, routine coronary angiography, as advocated by Hertzer[6] and Hertzer et al.[11] does not appear to be necessary or appropriate in this setting.

3. *Extensive preoperative preparation.* Preoperative evaluations of pulmonary function and renal disease, formal aortography, and the routine placement of a preoperative Swan-Ganz catheter permits maximizing prophylactic and early therapeutic management of potentially serious complications. We have followed the suggestions of Ruby et al.[12] and Whittemore et al.[13] throughout this series and firmly believe they have been very important adjuncts in the intraoperative and early postoperative management of many of these patients.

4. *Expeditious surgery.* The availability of the Gomez self-retaining retractor, minimizing the need for assistance and erratic retraction, routine use of the cell saver, administration of autologous blood, and minimal dissection have decreased blood loss and expedited surgery. The average operating time of 2.5 hours in an institution heavily committed to a vascular fellowship training program documents the resulting advantages in patient care. Alternative procedures, such as induced aneurysm thrombosis and peripheral bypass, as advocated by Leather et al.[14] do not seem necessary as emphasized by Schwartz et al.,[15] since the operative morbidity rate for elective resection can be decreased to under 1% despite the presence of serious multisystem compromise and advanced age in many patients.

5. *Aggressive postoperative care.* Problems of hemodynamic stability, respiratory function and renal function are pursued with vigor during the early postoperative period.

6. *Antibiotic prophylaxis.* The routine use of preoperative, intraoperative, local operative, and postoperative antibiotics appears to have minimized wound and other infectious problems. In the entire series there has been no instance of graft infection or of serious wound infection.

7. *Regular or routine postoperative follow-up.* The computerized vascular registry permits identification of patients' current status on a continuing basis. Patients who have not returned for routine follow-up visits are contacted regarding their current status in a regularized fashion. This permits periodic surveys of the late complications of surgical treatment and allows monitoring and continuing care of associated medical problems. In addition, it provides the surgeon with a continuing stream of information regarding the surgeon's own experience, problems, and late results.

Conclusions

A consecutive series of 123 patients with abdominal aortic aneurysms were subjected to elective or urgent surgery with a mortality rate of 0.8% and overall 5-year survival rate of 72%. These results attest to improvements in our ability to select patients for elective surgery and perform such procedures with a low risk rate. In addition, the earlier diagnosis of these lesions simplifies the surgical approach, permitting the use of tube grafts in 50% of the patients. No late complications of iliac aneurysm enlargement were detected in this series as a result of this policy. Elective aneurysm surgery is now capable of achieving late survival rates approaching those of the normal population despite the presence of significant concomitant cardiovascular, pulmonary, and renal disease.

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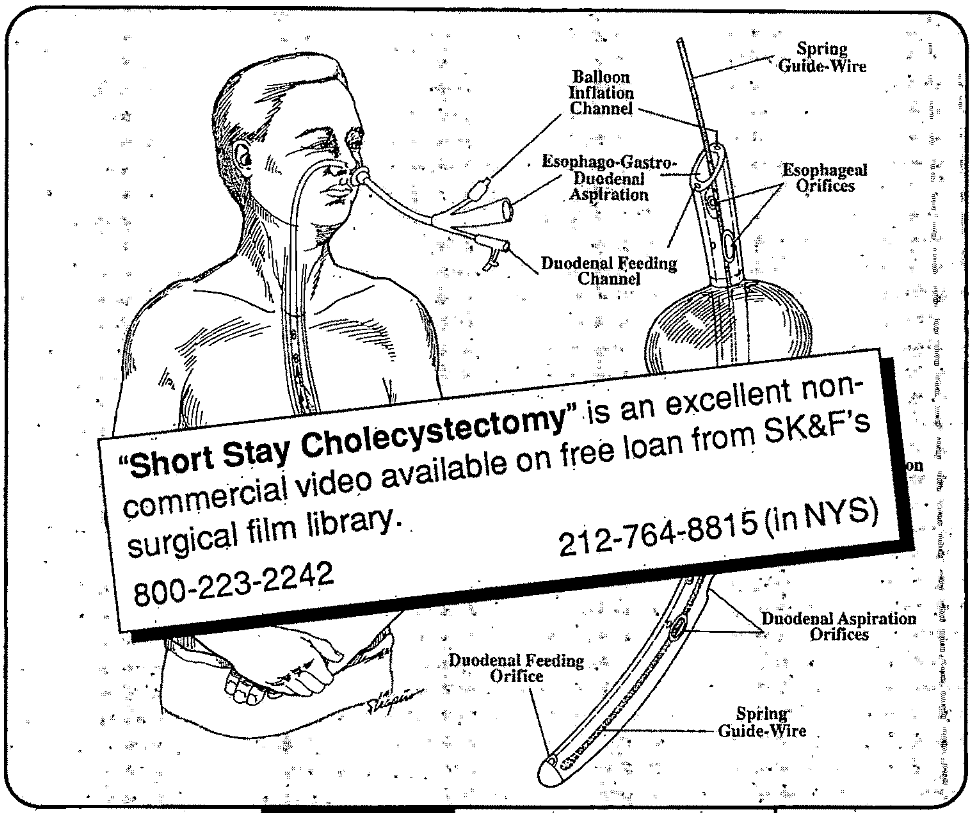

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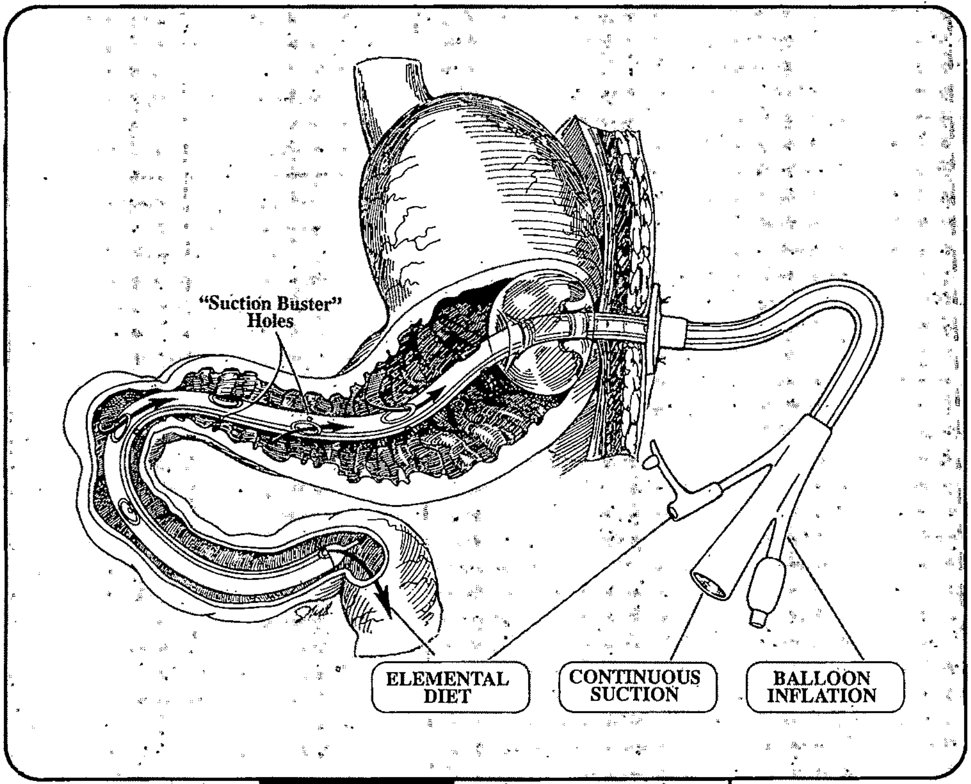

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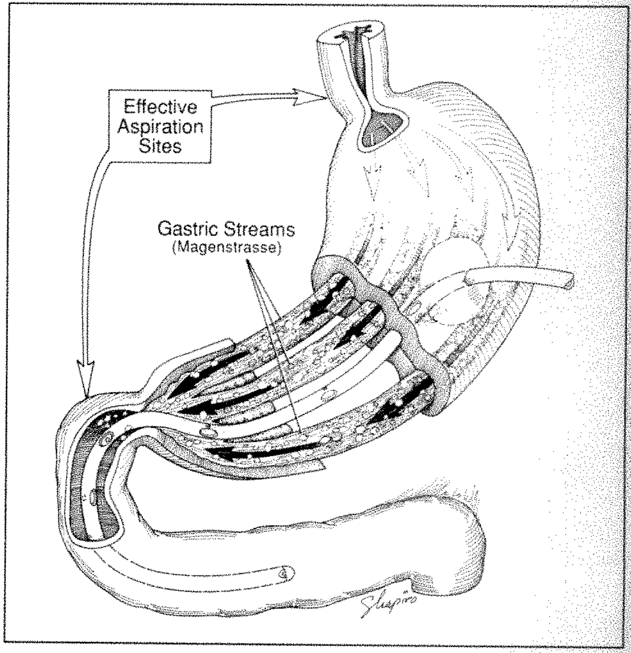

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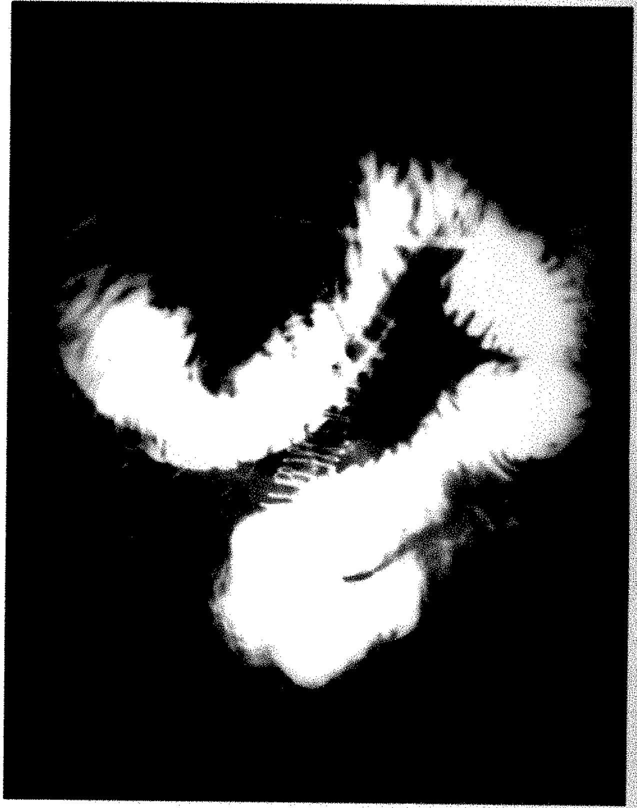

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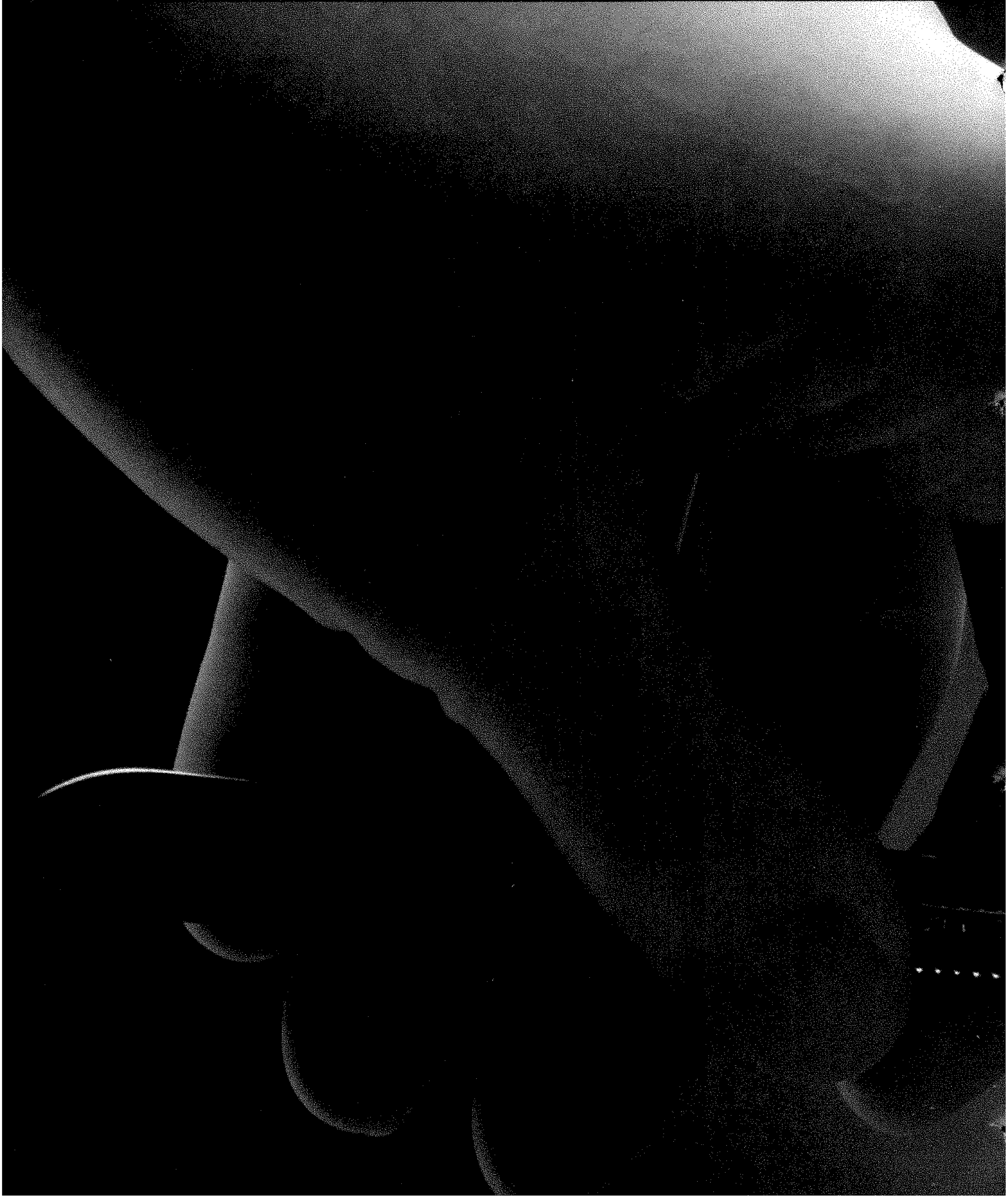

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PRIMAXIN is contraindicated in patients who have shown hypersensitivity to any component of this product. Before initiating therapy with PRIMAXIN, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams, and other allergens. If an allergic reaction to PRIMAXIN occurs, discontinue the drug. Serious hypersensitivity reactions may require epinephrine and other emergency measures.

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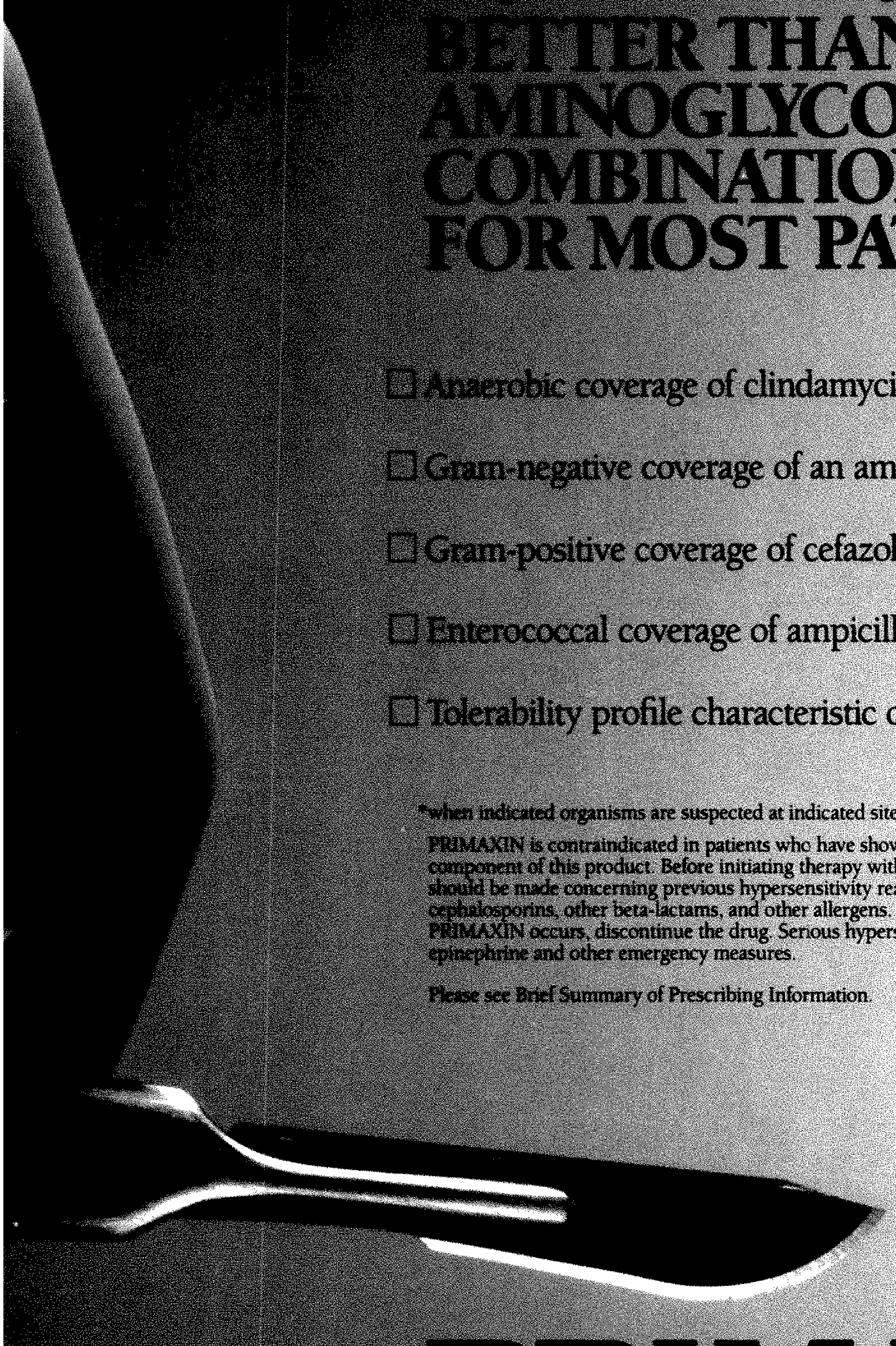

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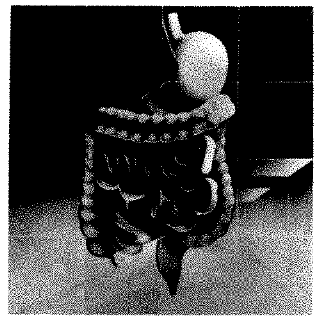

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Warnings: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH BETA LACTAMS. THESE REACTIONS ARE MORE APT TO OCCUR IN PERSONS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER BETA LACTAM. BEFORE INITIATING THERAPY WITH 'PRIMAXIN,' CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA LACTAMS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION TO 'PRIMAXIN' OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with virtually all antibiotics, including PRIMAXIN; therefore it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. This colitis may range in severity from mild to life threatening.

Mild cases of pseudomembranous colitis may respond to drug discontinuance alone. In more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte, and protein supplementation, and the use of a drug such as oral vancomycin, as indicated. Isolation of the patient may be advisable. Other causes of colitis should also be considered.

Precautions: *General*—CNS adverse experiences such as confusional states, myoclonic activity, and seizures have been reported during treatment with PRIMAXIN, especially when recommended dosages were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. However, there have been reports of CNS adverse experiences in patients who had no recognized or documented underlying CNS disorder or compromised renal function.

Patients with severe or marked impairment of renal function, whether or not undergoing hemodialysis, had a higher risk of seizure activity when receiving maximum recommended doses than those with no impairment of renal function; therefore, maximum recommended doses should be used only where clearly indicated (see DOSAGE AND ADMINISTRATION).

Patients with creatinine clearances of $\leq$5 mL/min/1.73 m^2 should not receive PRIMAXIN unless hemodialysis is instituted within 48 hours.

For patients on hemodialysis, PRIMAXIN is recommended only when the benefit outweighs the potential risk of seizures.

Close adherence to the recommended dosage and dosage schedules is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of PRIMAXIN re-examined to determine whether it should be decreased or the antibiotic discontinued.

As with other antibiotics, prolonged use of PRIMAXIN may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken. While PRIMAXIN possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system function during prolonged therapy is advisable.

Drug Interactions—Since concomitant administration of PRIMAXIN and probenecid results in only minimal increases in plasma levels of imipenem and plasma half-life, it is not recommended that probenecid be given with PRIMAXIN.

PRIMAXIN should not be mixed with or physically added to other antibiotics. However, PRIMAXIN may be administered concomitantly with other antibiotics, such as aminoglycosides.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Gene toxicity studies were performed in a variety of bacterial and mammalian tests *in vivo* and *in vitro*. The tests were: V79 mammalian cell mutation assay (PRIMAXIN alone and imipenem alone), Ames test (cilastatin sodium alone), unscheduled DNA synthesis assay (PRIMAXIN), and *in vivo* mouse cytogenicity test (PRIMAXIN). None of these tests showed any evidence of genetic damage.

Reproduction tests in male and female rats were performed with PRIMAXIN at dosage levels up to 8 times the usual human dose. Slight decreases in live fetal body weight were restricted to the highest dosage level. No other adverse effects were observed on fertility, reproductive performance, fetal viability, growth, or postnatal development of pups. Similarly, no adverse effects on the fetus or on lactation were observed when PRIMAXIN was administered to rats late in gestation.

- *Pregnancy*—Pregnancy Category C: Teratogenicity studies with cilastatin sodium in rabbits and rats at 10 and 33 times the usual human dose, respectively, showed no evidence of adverse effect on the fetus. No evidence of teratogenicity or adverse effect on postnatal growth or behavior was observed in rats given imipenem at dosage levels up to 30 times the usual human dose. Similarly, no evidence of adverse effect on the fetus was observed in teratology studies in rabbits with imipenem at dosage levels at the usual human dose.

Teratology studies with PRIMAXIN at doses up to 11 times the usual human dose in pregnant mice and rats during the period of major organogenesis revealed no evidence of teratogenicity.

Data from preliminary studies suggest an apparent intolerance to PRIMAXIN (including emesis, inappetence, body weight loss, diarrhea, and death) at doses equivalent to the average human dose in pregnant rabbits and cynomolgus monkeys that is not seen in non-pregnant animals in these or other species. In other studies, PRIMAXIN was well tolerated in equivalent or higher doses (up to 11 times the average human dose) in pregnant rats and mice. Further studies are under way to evaluate these findings.

There are, however, no adequate and well-controlled studies in pregnant women. PRIMAXIN should be used only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRIMAXIN is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in infants and children below 12 years of age have not yet been established.

Adverse Reactions: PRIMAXIN is generally well tolerated. Many of the 1,723 patients treated in clinical trials were severely ill and had multiple background diseases and physiological impairments, making it difficult to determine causal relationship of adverse experiences to therapy with PRIMAXIN.

Local Adverse Reactions—Local adverse clinical reactions that were reported as possibly, probably, or definitely related to therapy with PRIMAXIN were: phlebitis/thrombophlebitis (3.1%), pain at the injection site (0.7%), erythema at the injection site (0.4%), vein induration (0.2%), infused vein infection (0.1%).

Systemic Adverse Reactions—The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to PRIMAXIN were: nausea (2.0%), diarrhea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%) (see PRECAUTIONS), dizziness (0.3%), pruritus (0.3%), urticaria (0.2%), somnolence (0.2%).

Additional adverse systemic clinical reactions reported as possibly, probably, or definitely drug related occurring in less than 0.2% of the patients or reported since the drug was marketed are listed within each body system in order of decreasing severity: *Gastrointestinal*—pseudomembranous colitis (see WARNINGS), hemorrhagic colitis, gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, heartburn, pharyngeal pain, increased salivation; *CNS*—encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, psychic disturbances; *Special Senses*—transient hearing loss in patients with impaired hearing, tinnitus; *Respiratory*—chest discomfort, dyspnea, hyperventilation, thoracic spine pain; *Cardiovascular*—palpitations, tachycardia; *Renal*—oliguria/anuria, polyuria; *Skin*—erythema multiforme, facial edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae; *Body as a Whole*—polyarthralgia, asthenia/weakness.

Adverse Laboratory Changes—Adverse laboratory changes without regard to drug relationship that were reported during clinical trials or reported since the drug was marketed were: *Hepatic*—increased SGPT, SGOT, alkaline phosphatase, bilirubin, and LDH; *Hemic*—increased eosinophils, positive Coombs test, decreased WBC and neutrophils, including agranulocytosis, increased WBC, increased platelets, decreased platelets, decreased hemoglobin and hematocrit, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils; *Electrolytes*—decreased serum sodium, increased potassium, increased chloride; *Renal*—increased BUN, creatinine; *Urinalysis*—presence of urine protein, urine red blood cells, urine white blood cells, urine casts, urine bilirubin, and urine urobilinogen.

NOTE: Due to the high antimicrobial activity of PRIMAXIN, it is recommended that the maximum total daily dosage not exceed 50 mg/kg/day or 4.0 g/day, whichever is lower.

How Supplied: PRIMAXIN is supplied as a sterile powder mixture in vials, infusion bottles, and single-dose ADD-Vantage®[†] vials containing imipenem anhydrous and cilastatin sodium as follows: 250 mg imipenem equivalent and 250 mg cilastatin equivalent; 500 mg imipenem equivalent and 500 mg cilastatin equivalent.

Caution: The suspension from vials is not for direct infusion.

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The Acute Surgical Abdomen after Cardiac Surgery Involving Extracorporeal Circulation

ALEXANDER S. ROSEMURGY, M.D., EARL McALLISTER, M.D., and RICHARD C. KARL, M.D.

From 1972 through 1984, 7140 cardiac operations were performed at one university teaching hospital; they were reviewed to elucidate common factors in patients developing an acute surgical abdomen after cardiac surgery and extracorporeal circulation. Twenty-one patients (0.29%) developed an acute surgical abdomen in the period following cardiac surgery. The abdominal surgical complications were, in general, due to complications of peptic ulcer disease, decreased intestinal blood flow, and cholecystitis. There was no correlation between preoperative history, physical examination, cardiac function, laboratory data, and the subsequent development of an acute abdomen. Mortality rate, 24% after abdominal surgery, was increased with emergency cardiac operations, combined cardiac procedures, complications of cardiac surgery, unnecessary delay of abdominal surgery, and abdominal wound complications. Major abdominal wound complications were seen in 38%. Patients undergoing cardiac surgery may develop a variety of common abdominal surgical disorders. Patients so inclined cannot be identified prior to cardiac surgery. Ulcer prophylaxis, wound management, prompt resuscitation, and timely surgery are critical.

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THE ACUTE SURGICAL ABDOMEN following cardiac surgery and extracorporeal circulation is a serious, though infrequent, development. Over the past 20 years several authors have addressed the subject of *general surgical* complications after open-heart surgery.[1-3] These have been small series generally involving nonoperative complications. Hyperbilirubinemia, pancreatitis, gastrointestinal bleeding, and nonspecific abdominal pain have frequently been noted as the general surgical complications.[1,4,5] Few studies, each involving no more than a handful of patients, have addressed the acute surgical abdomen following cardiac operations involving cardiopulmonary bypass.[6,7]

We undertook this study involving a large number of patients to determine the type and frequency of intra-abdominal catastrophies that occur after cardiac surgery involving extracorporeal circulation. Specifically, we set out to find common factors in patients who develop an acute surgical abdomen after cardiac surgery. Additionally, we sought to characterize a subgroup of patients undergoing cardiac surgery that are prone to develop an acute surgical abdomen to enable us to diagnose the abdominal condition earlier or, ideally, to prevent the acute surgical abdomen from occurring in this setting.

Materials and Methods

Between January 1, 1972 and June 1, 1984, 7140 patients underwent cardiac surgery involving extracorporeal circulation at one university teaching program. These patients form the basis of this retrospective review. Data were obtained from medical records, operative reports, surgical pathology reports, and attending surgeon records.

The hospital course of each patient was reviewed for the following parameters. The patient's health prior to cardiac surgery was evaluated through history and physical examination, routine laboratory testing, and objective tests of cardiac performance (*e.g.*, muga scans). Details concerning the cardiac operation were sought, including the number and type of procedures performed at each cardiac operation, the duration of extracorporeal circulation, and the duration of aortic occlusion. Signs and symptoms of abdominal disease in the period after cardiac surgery were sought. Pertinent laboratory tests and diagnostic studies were reviewed. Details of the abdominal operations were assessed; postoperative notes, pathology reports, and operative reports were reviewed. Intraoperative findings, operative procedures, and postoperative morbidity and mortality rates were reviewed. Patient follow-up continued until patient death or until resolution of the abdominal disorder.

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Submitted for publication: September 17, 1987.

TABLE 1. *The Number of Patients who Underwent Cardiac Surgery and Subsequently Developed an Acute Surgical Abdomen*

Year	Valve	Bypass	Acute Abdomen	Incidence (%)
1972	23	19	0	0.00
1973	39	23	0	0.00
1974	98	165	0	0.00
1975	122	209	2	0.60
1976	143	245	0	0.00
1977	143	271	0	0.00
1978	153	334	1	0.21
1979	187	589	0	0.00
1980	236	782	1	0.10
1981	161	653	5	0.61
1982	217	1176	3	0.22
1983	251	717	3	0.31
June 1984	36	149	6	3.24
Total	1809	5332	21	0.29

Results

Twenty-one patients (0.29%), 13 males and 8 females, with an average age of 66 years (range: 44–78 yr) developed an acute surgical abdomen after cardiac surgery and extracorporeal circulation. Twenty-three abdominal operations were performed on this group. Eighteen patients developed this complication since January 1980 (Table 1).

Review of the medical histories of the 21 patients was largely unremarkable. One patient had a history of peptic ulcer disease and two had a history of cholelithiasis. Review of the admission physical examinations revealed that one patient had an inguinal hernia at admission. None of the 21 patients had a rectal exam nor had stool tested for occult blood upon admission.

Arterial blood gas analysis was not performed upon five patients prior to cardiac surgery. Two patients had arterial P_{CO_2} greater than 50 torr, and two patients had arterial PO_2 less than 60 torr. Elevated serum creatine levels were noted in eight patients (38%), and elevated serum alkaline phosphate levels were noted in nine patients (43%) at admission. Only one patient had a hematocrit less than 35%. One patient had a minimally elevated bilirubin. The mean ejection fraction for the 21 patients was 62%, with a range of 35–89%.

Ten of the 21 patients (48%) that developed an acute surgical abdomen after cardiac surgery did so after elective aortocoronary bypass grafting (Table 2). One third of the patients underwent elective combined cardiac procedures involving more than one of the following: aortocoronary bypass grafting, cardiac valve replacement, ventricular aneurysmectomy, and atrial septal defect repair (Table 2). One patient underwent a complex *redo valve* replacement in the course of having multiple valves replaced. There were three emergency operations. Patients undergoing combined cardiac procedures prior to developing an acute surgical abdomen had longer *pump times* (mean ± SEM; 131 ± 17 min, 81 ± 5 min; $p < 0.05$) than patients undergoing a single cardiac procedure.

TABLE 2. *Cardiac Operations that Preceded the Development of an Acute Surgical Abdomen in 21 Patients*

	N
Elective aortocoronary bypass grafting	10
Emergency aortocoronary bypass grafting	2
Elective bypass grafting with aneurysmectomy and pacemaker placement	1
Elective valve replacement and bypass grafting	3
Emergency valve replacement and bypass grafting	1
Elective multiple valve replacement (1 *redo*)	2
Elective ASD repair	1
Elective ASD repair and valve replacement	1

The hospital course following cardiac surgery and preceding the development of an acute surgical abdomen for the 21 patients in this series could easily be divided into two groups. The first group, six patients, had an uneventful course after cardiac surgery before developing an acute surgical abdomen. Of these 6 patients, 3 developed complications of peptic ulcer disease (2 hemorrhage, 1 perforation), 1 developed an intestinal infarction, 1 developed a sigmoid colon perforation, and 1 underwent a nondiagnostic laparotomy. This last patient was later reoperated on and found to have intestinal ischemia with an infarcted perforated cecum. Intestinal ischemia with infarction in this patient was believed to be due to a low flow state, which persisted after the nondiagnostic laparotomy.

Each of the remaining 15 patients experienced a complex course with major complications after cardiac surgery prior to developing an acute surgical abdomen. The three patients who had undergone emergency cardiac operations were in this group. Seven of the 15 patients developed eight complications that were directly attributable to their cardiac surgery; 3 patients developed sternal infections with mediastinitis, 2 patients experienced excessive bleeding that did not require reoperation, and 3 patients experienced excessive bleeding that did require reoperation, 2 because of cardiac tamponade. In each of these seven patients, these complications preceded complications experienced by all 15 patients of this group prior to the onset of an acute surgical abdomen: renal failure, prolonged ileus, respiratory failure, stroke, hemorrhagic shock, cardiogenic shock, and sepsis. In general, the 15 patients who experienced complex courses after cardiac surgery developed acute surgical abdomens due to complications of peptic ulcer disease, deceased intestinal blood flow, and cholecystitis (Table 3).

In the series of 21 patients as a whole, 6 patients developed an acute surgical abdomen because of complications of peptic ulcer disease; 2 died. Five patients developed an acute surgical abdomen because of colonic perforations; 1 died. Four patients developed an acute

TABLE 3. *Causes of Acute Surgical Abdomen Leading to Celiotomy in 15 Patients Having a Complex Course After Cardiac Surgery*

	N
Foregut infarction (2 deaths)	3
Sigmoid colon perforation	3
Acalculus cholecystitis	2
Complications of peptic ulcer disease	
Bleeding (1 death)	3
Perforation (1 death)	2
Incarcerated femoral hernia	1
Gastric perforation	1
Ischemic cecal perforation	1
Ischemic sigmoid colitis	1

surgical abdomen because of intestinal infarction; 2 died. Two patients developed an acute surgical abdomen because of acalculus cholecystitis leading to cholecystectomy and in 2 other patients calculus cholecystitis was concomitantly noted at celiotomy, leading to cholecystostomy (Table 4).

None of the six patients who developed an acute surgical abdomen due to complications of peptic ulcer disease were on antiulcer medication after cardiac surgery. Four of the six patients had a history of ulcer disease, had post pump complications (mediastinitis, excessive bleeding after cardiac surgery), or were taking aspirin. Two of the six patients (33%) died, including one who experienced reperforation of an ulcer.

The underlying cause of the eventual acute surgical abdomen in three patients was noted at the admission medical history or physical examination. One patient with a history of peptic ulcer disease experienced perforation of a peptic ulcer after cardiac surgery leading to an acute surgical abdomen. One patient with a history of cholelithiasis developed cholecystitis and a subsequent *low flow state* leading to an ischemic perforated cecum. Another patient, noted to have an inguinal hernia upon admission physical examination, developed an incarcerated inguinal hernia leading to an acute surgical abdomen in the period following cardiac surgery. Alternatively, 18 patients developed an acute surgical abdomen, which, by the admission history and physical examination alone, was unexpected.

Complications occurred after the abdominal operations. Abdominal wound sepsis was seen in 8 of 21 patients (38%). This is despite death in two patients hours after abdominal surgery. Excluding these two patients, wound sepsis was seen in 8 of 19 patients (42%). In each case wound sepsis prolonged hospitalization. In 3 of these 8 patients (38%) incisional dehiscence developed, and 2 of these 8 patients (25%) died.

Cerebrovascular accidents (5%), obstructive uropathy (5%), congestive heart failure (14%), nutritional depletion (14%), respiratory failure (26%), and sepsis (38%) with multiorgan failure (10%) were noted to develop after the abdominal operations.

TABLE 4. *Abdominal Disorders Leading to Acute Surgical Abdomen in 21 Patients*

	N
Complications of peptic ulcer disease (2 died)	6
Colonic perforation: (1 died)	5
Bowel infarction: (2 died)	4
Acalculus cholecystitis	2
Incarcerated femoral hernia	1
Ischemic sigmoid colitis	1
Gastric perforation	1
Negative laparotomy–infarcted perforated cecum	1

The overall mortality rate in this series was 24%. Death was due to multiorgan failure and sepsis in four patients and a massive myocardial infarction in one patient. When the abdominal operation was delayed for more than 24 hours after the recognition of an acute surgical abdomen, the mortality rate was 75% (3 of 4 patients). Emergency cardiac operations, combined cardiac procedures, post pump complications (*e.g.*, cardiac tamponade, bleeding, and mediastinitis), and a complex course after cardiac surgery prior to developing an acute surgical abdomen were all associated with higher mortality rates in patients who developed an acute surgical abdomen after cardiac surgery involving extracorporeal circulation (Table 5).

Discussion

The development of an acute surgical abdomen after cardiac operations involving extracorporeal circulation is an infrequent complication with significant morbidity and mortality rates. Such a development is not a phenomenon unique to the *pioneer* days of cardiac surgery and extracorporeal circulation. In this review, the incidence of the acute surgical abdomen after cardiac operations was nearly four times greater after 1980 than in the years prior to 1980.

Admission histories and physical examinations were neither complete nor exhaustive. Laboratory evaluation, similarly, was generally incomplete. Data available reflect an older population with medical problems, quite consistent with the age, sex, and general fair health of patients undergoing cardiac surgery. The ejection frac-

TABLE 5. *The type of Cardiac Operation and Course after Cardiac Surgery as It Relates to Mortality Rates Associated with the Subsequent Acute Surgical Abdomen*

3 Emergency cardiac operations	1 Death (33%)
18 Elective cardiac operations	4 Deaths (22%)
8 Combined cardiac procedures	3 Deaths (38%)
13 Single cardiac procedures	2 Deaths (15%)
7 Post pump complications	3 Deaths (43%)
14 No post pump complications	2 Deaths (14%)
6 Smooth course after cardiac surgery	0 Deaths (0%)
15 Complex course after cardiac surgery	5 Deaths (33%)

Overall mortality rate: 24%

tions of patients in this study were generally good prior to cardiac surgery.

Preoperative medical histories and physical examinations, laboratory data, and tests of cardiac function as performed were not helpful in predicting the subsequent development of an acute surgical abdomen. There appears to be no common factors among patients who develop an acute surgical abdomen after cardiac surgery. For the purpose of early diagnosis or prevention, we were additionally unable to characterize a subgroup of patients undergoing cardiac surgery who were prone to developing an acute surgical abdomen.

The patients in this review could conveniently be divided into two groups depending upon their course after their cardiac operation. The morbidity and mortality rates of these groups was significantly different. Those six patients with an uneventful course after cardiac surgery prior to the sudden development of an acute surgical abdomen experienced no mortality. The acute surgical abdomen in these patients was generally due to complications of peptic ulcer disease or low intestinal blood flow. The other 15 patients experienced a very complex course after their cardiac operation. All of these patients developed major medical problems such as renal failure, sepsis, hemorrhagic shock, cardiogenic shock, and cerebrovascular accidents prior to the development of their acute surgical abdomen. A subgroup of seven patients had additional problems, including mediastinitis, sternal infections, and excessive post pump bleeding, all attributable to their cardiac operation directly. The mortality rate in this group of 15 patients was very high (33%), in contrast to the patients with an uneventful course after cardiac surgery prior to developing an acute surgical abdomen (0%).

Major medical problems and post pump complications should be sought when patients suspected of having an acute surgical abdomen after cardiac surgery are encountered. These problems and complications are associated with a high mortality rate in this setting. Cardiac operations that are done as emergency procedures, cardiac operations that consist of combined procedures (and prolonged extracorporeal perfusion), and reoperative cardiac operations are cardiac operations that are associated with a poor prognosis in patients who subsequently develop an acute surgical abdomen. Delay in performing abdominal surgery once an acute surgical abdomen is recognized is associated with a prohibitive mortality rate.

There is a plethora of complications that can occur after abdominal surgery. Sepsis is a frequent and grave complication. Wound complications are also frequent. Wound care must be taken very seriously after abdominal surgery in these patients. Incision placement must be well thought out prior to abdominal surgery. Locations for potential stomas should be marked preoperatively to ensure acceptable placement and optimal daily care postoperatively. There should be no pressure to perform primary wound closures; delayed primary closures should be frequently utilized. Wounds that are left open should be aggressively cared for and debrided frequently. In this setting wound dressings should be changed frequently, and evidence of wound sepsis should be continuously sought.

In this review the abdominal causes of the acute surgical abdomens were not unusual abdominal disease processes. These processes are the common general surgical problems that are seen in most every surgical practice. *Fascinomas* were not encountered. In general, the abdominal disorders that resulted in the development of the acute surgical abdomen were due to altered intestinal blood flow, peptic ulcer disease, cholecystitis, and intestinal perforation.

Patients with an ulcer history, patients who have a particularly stressful course after cardiac surgery, and patients who require aspirin treatment after cardiac surgery should have antiulcer medications routinely after cardiac surgery.

When caring for patients suspected of having an acute surgical abdomen after cardiac surgery, several factors must be kept in mind. Patients must undergo an aggressive, though directed, workup to diagnose the abdominal process causing the suspected acute surgical abdomen. Surgery must be performed promptly when indicated. Abdominal surgery should be delayed only for prompt and aggressive resuscitation; unnecessary delay is accompanied by unacceptable mortality rates. It is not acceptable to deem patients *too sick to operate on* since patients after cardiac revascularization are more suitable for abdominal surgery than prior to their cardiac surgery.[8] Furthermore, patients in this setting are not likely to become more suitable candidates for surgery with the unnecessary passage of time. Arteriograms and other invasive diagnostic studies should not be used unless therapeutic decisions will be based on their results.

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Gastric Mucosal Blood Flow in Misoprostol Pretreated Aspirin-induced Ulceration

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To determine whether topical misoprostol (a synthetic PGE$_1$ analog) pretreatment will increase or prevent a decrease in gastric mucosal blood flow (GMBF) during topical aspirin administration, we studied focal GMBF simultaneously by hydrogen gas clearance in a split canine gastric chamber model with one side as control. In the test chamber, immediately after topical misoprostol, there was a transient and significant increase (18%) in GMBF (55.71 ± 7.80 to 65.84 ± 6.12 mL/min/100 g; $p < 0.05$). After 15 minutes, GMBF returned to premisoprostol levels and then showed a graded drop throughout the aspirin and postaspirin periods. No grossly visible mucosal lesions were observed. In the control chamber, mucosal lesions were observed 45 minutes after aspirin administration accompanied by a graded drop in GMBF throughout the experiments. Misoprostol neither produced a sustained increase in GMBF nor prevented the subsequent reduction in GMBF induced by aspirin. Therefore, maintenance of GMBF may not be important in cytoprotection by misoprostol. The sustained nonparietal secretion induced by this synthetic PGE$_1$ analog may be important in gastric cytoprotection.

THE PRECISE MECHANISM(S) of gastric cytoprotection by prostaglandins (PG) is not known. The circulatory hypothesis proposes that the cytoprotective action is mediated through an increase in gastric mucosal blood flow (GMBF).[1-7] This hypothesis has, however, been faced with problems including (1) the results of studies of the effects of PG on GMBF have been inconsistent[3]; (2) though a number of the A, E, and I PG increase GMBF,[3,8-10] PGF$_{2\alpha}$, also cytoprotective,[11,12] is a known vasoconstrictor[8,13-16]; and (3) 16,16-dimethyl PGE$_2$ has been reported to prevent ulcer formation in the absence of arterial perfusion in isolated canine gastric mucosa,[17] in amphibian gastric mucosa *in vitro,*[18] and in gastric cell cultures in rats.[19,20]

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Misoprostol is a synthetic PGE$_1$ analog that has been reported to have both gastric antisecretory and cytoprotective properties.[21-30] There have been few reports in the literature on the effects of misoprostol on gastric blood flow. While some investigators have reported an increase in total gastric blood flow[2] and gastric mucosal blood volume,[31] others have reported either a decrease in total GMBF[23] or no effect.[27] We designed this study to elucidate further the circulatory hypothesis by a controlled investigation of focal GMBF changes using the hydrogen gas clearance (HGC) technique before, during, and after misoprostol pretreatment of aspirin-induced mucosal injury in a canine chambered gastric segment model. Specifically, the aim of this study was to test the hypothesis that pretreatment of the gastric mucosa with an antisecretory dose of misoprostol would increase or maintain gastric mucosal blood flow during aspirin injury. Second, the fluid and ionic fluxes were measured to determine any interrelationship between GMBF, fluid/ionic fluxes, and gastric cytoprotection.

Materials and Methods

Surgical Preparation

Four adult mongrel dogs of either sex, weighing 20–30 kg, were anesthetized with sodium pentobarbital (25 mg/kg) after a 24-hour fast (only water *ad libitum*). The dogs were intubated and maintained on a Harvard respirator (Harvard Apparatus, South Natick, MA) throughout each experiment. A hind leg vein was cannulated with a polyethylene catheter (PE 200) for infusion of 0.9% sodium chloride for the maintenance of hydration and a stable blood pressure. Arterial blood pressure was directly monitored by a saline-filled polyethylene cath-

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eter (PE 200) in the left femoral artery via a Statham Gould P 23 Db transducer (Gould Statham Instruments Inc., Hato Ray, Puerto Rico). Following a midline laparotomy and splenectomy, a split chambered segment model of the gastric corpus with an isolated vascular pedicle was prepared according to the method of Moody and Durbin.[32] This model permits the use of one side of the chamber as test, the other as control and provides gastric mucosal surface of 17 cm^2 in each side. We have shown that electrode-mucosa contact is not a problem in this experimental model.[33] Body temperature and the temperature of the preparation were maintained by an electric blanket and infrared lamps. The preparation was allowed to stabilize for 60 minutes after surgery.

Experimental Design

Focal GMBF measurements were performed once every 15-minutes by two HGC electrodes placed in contact with the mucosa in each lumen of the chamber. One electrode was located in the upper and the other in the lower quadrants of each lumen throughout the experiments. Once the electrodes had been located at the beginning of each experiment there was no relocation throughout the experiments. Bathing solutions (8 mL) were instilled into and recovered from each lumen every 15-minutes as follows:

Test chamber. (1) basal periods (60 min): 100 mmol/L HCl + 50 mmol/L NaCl; (2) misoprostol periods (30 min): 100 mmol/L HCl + 50 mmol/L NaCl + 1 mL misoprostol (200 μg); (3) aspirin periods (60 min): 100 mmol/L HCl + 50 mmol/L NaCl + 20 mmol/L aspirin; and (4) postaspirin periods (120 min): same as for the basal periods.

Control chamber. Solutions instilled were the same as for the test chamber except in (2) where instead of misoprostol, 1 mL of vehicle (0.2 mL absolute ethanol + 0.8 mL phosphate buffer) was added to HCl and NaCl. Laboratory assays were performed on the recovered bathing solutions to determine the changes in volume, pH, sodium, and hydrogen ion concentrations. The pH of the bathing solutions and hydrogen ion concentration (titratable acid) were measured using a pH meter (Radiometer Copenhagen, Bach-Simpson Ltd., London, Ontario, Canada). Titration of the recovered solutions were performed to pH 2, the pH of the instilled solutions, with 0.1 N NaOH. Sodium ion concentration was measured with a Nova 1 Na^+/K^+ analyzer (Nova Biomedical, Newton, MA). The difference between the product of concentration and volume for the instilled and recovered solutions per 15 minute periods are the net fluxes expressed for sodium and hydrogen ions in the results below.

Misoprostol Preparation

Misoprostol was received as neat chemical in dry ice (G.D. Searle and Co. Inc., Skokie, IL). It was dissolved in isotonic 20% ethanol-containing phosphate buffer (pH 7.4). The misoprostol stock-solution was stored in vials at below −20 C when not in use and allowed to thaw to room temperature before use.

Hydrogen Gas Clearance

This was performed by standard technique as described previously.[33,34] The four HGC electrodes (Unique Medical Co. Ltd., Tokyo) with the four reference Ag/AgCl skin electrodes (Red Dot, 3M Canada Inc., London, Ontario, Canada) were connected to a Beckman multichannel recorder (Beckman Type R Dynograph, Beckman Instruments Inc., Schiller Park, IL) to obtain a permanent record of the measurements.

Histology

Following the termination of each experiment the mucosa and submucosa of tissue from both chambers were quickly dissected from the underlying muscularis and immersed in 10% neutral buffered formalin. The mucosa-submucosa preparation was then spread out and pinned flat on a cork slab within the fixative. After 24 hours fixation the tissue was Swiss-rolled and stored in 70% ethanol. Three random slices from each roll were resected and processed through to either paraffin and stained with hematoxylin and eosin or embedded in glycol methacrylate and stained with methylene blue-basic fuchsin. The slides were coded and examined blindly. Several morphologic parameters were noted and/or recorded for each sample including mucosal height, number and spatial relationship of gastric glands, integrity and continuity of the epithelial sheet, and presence of inflammatory cells in the lamina propria, as well as the appearance of mucosal capillaries. The sections were organized into groups based on the morphologic analysis before the code was broken. Comparison of the groupings permitted evaluation of consistent morphologic features within and between each group.

Data Analysis

All data are expressed as mean ± SE. GMBF data are expressed in mL/min/100 g of tissue. Statistical analysis for significance at the 5% level was performed using either the paired Student's t test or ANOVA, and linear regression analysis. Because there is a significant difference in GMBF between the upper and lower quadrants of the gastric chamber model, in comparing flow values between the test and control chambers, they were paired upper *versus* upper and lower *versus* lower in the t-tests.

Results

Gross and Microscopic Appearance

In the test chamber, there was gross mucosal swelling within 5 minutes of topical application of 200 μg of misoprostol, a feature that persisted throughout the experimental period. No grossly visible lesions were observed either during or after aspirin administration. Mucosal integrity was maintained throughout the experiment except for an obvious increase in the amount of mucus adherent to the luminal surface. Histologic evaluation of the misoprostol-treated tissue revealed a swollen lamina propria giving the gastric glands a widely spaced appearance and increased mucosal height. There was no increase in cellularity of the mucosa. Vascular channels were easily identifiable, dilated but empty of any cellular components (Fig. 1).

In the control chamber, multiple focal punctate lesions appeared on the mucosa 45 minutes after aspirin administration. Mucosal swelling did not occur within this chamber. Typical aspirin-induced superficial erosions could be identified in localized areas (Fig. 2). Although the majority of the tissue exhibited a normal morphology, there was frequent observation of a widened zone of lamina propria just beneath the surface epithelium (Fig. 3).

Gastric Mucosal Blood Flow

Resting focal GMBF measured by the four HGC electrodes consecutively for 1 hour revealed a positional effect on blood flow in the four quadrants of the double-lumen chamber. In both test and control chambers, there was a highly significant difference between the

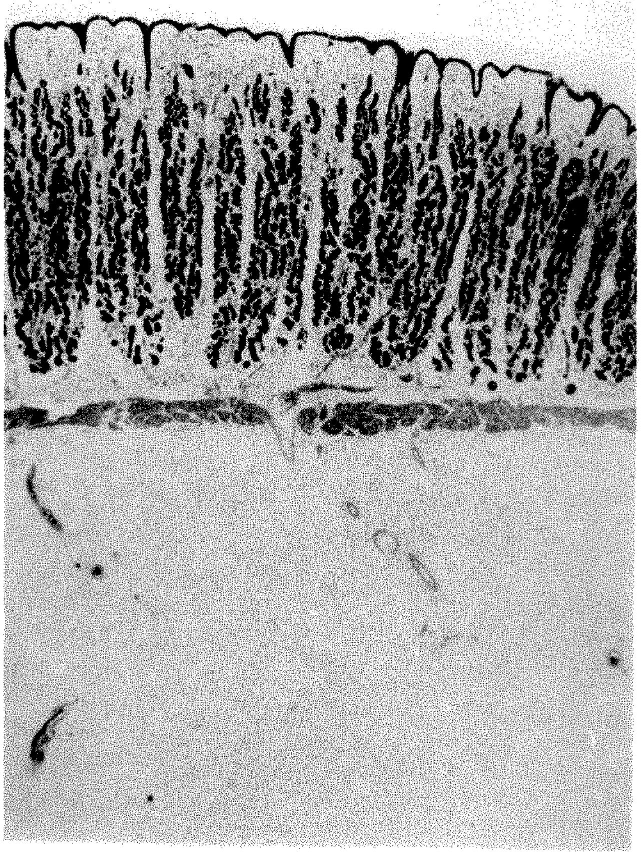
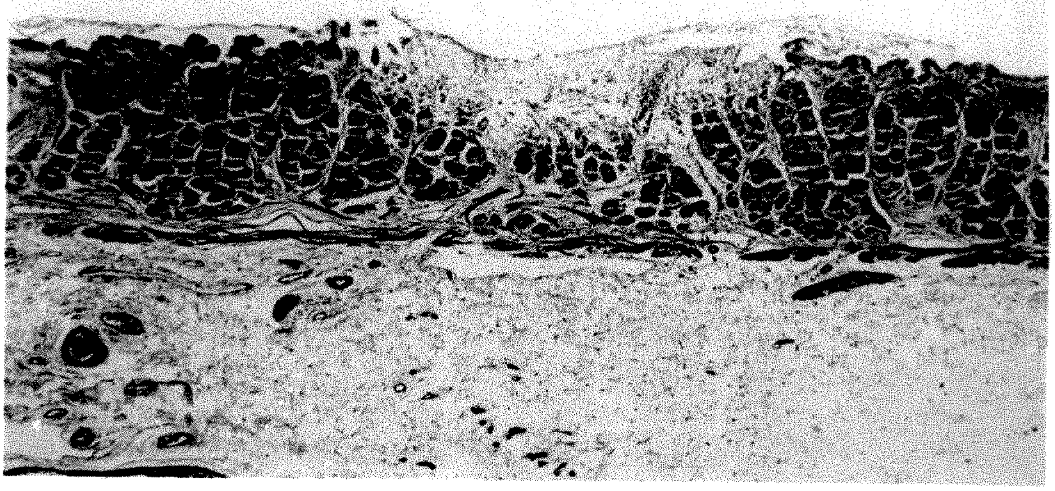


FIG. 1. Tissue from the test chamber illustrating the swollen, edematous appearance of the mucosa following misoprostol administration. The submucosa exhibits a similar reaction. Note the increased height of the mucosa when compared to Figure 2 (methacrylate, MBBF stain, original magnification ×100).

FIG. 2. A section through an aspirin-induced lesion in tissue from the control chamber. Areas adjacent to the lesion as well as the submucosa exhibit otherwise normal morphology (paraffin, hematoxylin and eosin, original magnification ×100).



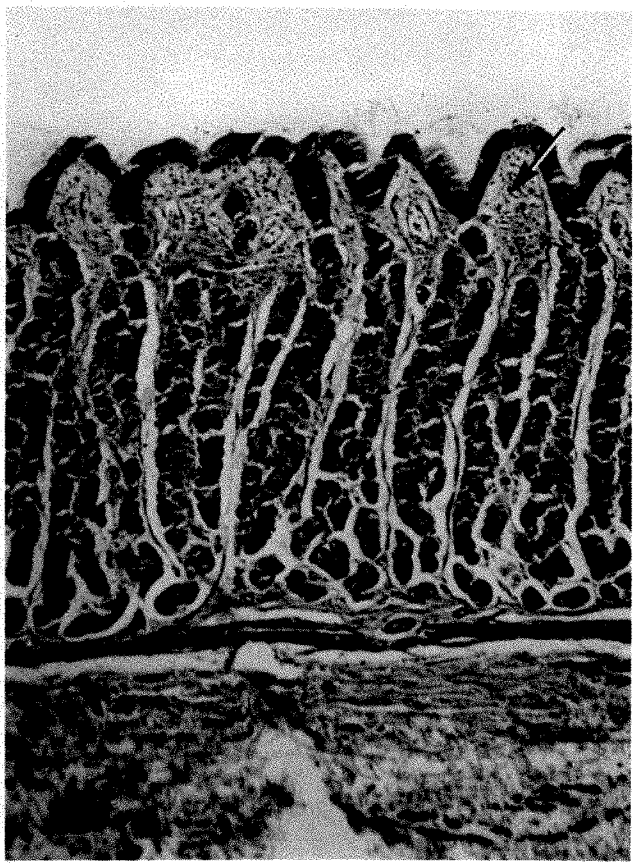


FIG. 3. Histologic appearance of the majority of tissue from the control chamber. Note the widened zone of lamina propria immediately beneath the surface epithelium (arrow) (paraffin, hematoxylin and eosin, original magnification ×160).

mean (± SE) resting GMBF values in the two upper and lower quadrants. Between the two chambers, there were no significant differences in the mean resting GMBF values recorded in the upper and lower quadrants (upper test: 66.31 ± 6.86; upper control: 63.66 ± 6.52; $p > 0.05$; lower test: 48.97 ± 4.08; lower control: 41.67 ± 3.45; $p > 0.05$; t-test). Linear regression analysis revealed a highly significant correlation between consecutive resting GMBF values recorded by the upper and lower electrodes located within each chamber (test: $r = 0.7511, N = 13, p < 0.01$; control: $r = 0.7151, N = 13, p < 0.01$), but consecutive resting GMBF values recorded by electrodes located on the same horizontal axis in the two chambers were not correlated.

Figure 4 depicts the simultaneous sequential changes in mean (±SE) GMBF values measured in the test and control chambers during the basal, misoprostol/control, aspirin, and postaspirin periods. In both chambers, the four consecutive mean GMBF values obtained in the basal periods were not significantly different from each other (test: 64.36 ± 10.77, 66.70 ± 9.36, 54.82 ± 7.54, and 55.71 ± 7.80; $p > 0.05$; control: 56.09 ± 6.23, 55.79 ± 7.99, 52.77 ± 9.53, and 48.37 ± 7.58; $p > 0.05$; ANOVA). In the test chamber immediately after the administration of misoprostol, there was a significant and transient increase (18%) in GMBF in the first misoprostol period above the final basal period mean flow value (from 55.71 ± 7.80 to 65.84 ± 6.12; $p < 0.05$; t-test). In the second misoprostol period, the mean GMBF value of 51.27 ± 6.10 was not significantly different from the final basal period mean flow value, indicating a return of GMBF to premisoprostol (basal) levels within 15 minutes even though administration of misoprostol was continued for an additional 15 minutes. After the misoprostol periods focal GMBF in the test chamber showed a graded drop throughout the aspirin periods, became significantly less than the final basal period mean flow value in the second aspirin period, and remained so until the end of the experiments. In the control chamber, there was a graded drop in GMBF throughout the aspirin periods, which became significantly different from the final basal period during the first postaspirin period and remained stable but significantly less than the basal period mean flow value in the remaining periods of the experiments.

Comparison of the simultaneous GMBF values obtained from the two chambers revealed no significant differences except during the first misoprostol/control period (test: 65.84 ± 6.12; control 41.43 ± 6.25; $p < 0.01$; t-test). In the second misoprostol/control period, though the mean GMBF value in the test chamber remained higher than in the control chamber, the difference was not significant statistically. Thereafter with aspirin, GMBF dropped in both chambers and re-

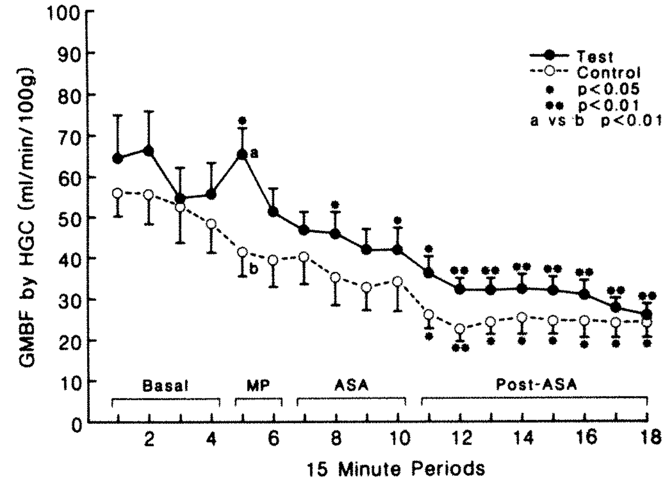


FIG. 4. The simultaneous sequential changes in mean (± SE) GMBF measured in the test and control chambers during the basal, misoprostol/control, aspirin and postaspirin periods. N = 8 for each point. Asterisks indicate significant differences from the final basal period mean (±SE) flow value within each chamber. MP = misoprostol/control periods; ASA = aspirin periods; HGC = hydrogen gas clearance.

TABLE 1. *Net Ionic and Fluid Fluxes in the Test and Control Gastric Chambers*

Periods	Flux Types	Test Chamber	Control Chamber	Test *Versus* Control P Value
Basal	Fluid (mL/15 min)	+0.02 ± 0.15	+0.09 ± 0.18	NS
	Na^+ (μmoL/15 min)	+79.91 ± 25.29	+95.63 ± 29.35	NS
	H^+ (μmoL/15 min)	−64.83 ± 15.69	−69.27 ± 17.38	NS
Misoprostol/control	Fluid (mL/15 min)	+3.36 ± 0.78*	+0.18 ± 0.28	<0.01
	Na^+ (μmoL/15 min)	+593.45 ± 103.21*	+171.42 ± 17.94	<0.01
	H^+ (μmoL/15 min)	−101.27 ± 27.65	−133.51 ± 35.99	NS
Aspirin	Fluid (mL/15 min)	+1.06 ± 0.29†	−0.49 ± 0.22	<0.01
	Na^+ (μmoL/15 min)	+213.52 ± 35.63†	−4.06 ± 11.11†	<0.001
	H^+ (μmoL/15 min)	+5.52 ± 12.02†	−20.53 ± 29.33	NS
Postaspirin	Fluid (mL/15 min)	+0.17 ± 0.07	−0.48 ± 0.11†	<0.001
	Na^+ (μmoL/15 min)	+84.28 ± 10.97	+26.52 ± 8.02†	<0.01
	H^+ (μmoL/15 min)	−45.49 ± 5.63	−88.30 ± 13.90	<0.01

Values are given as mean ± SE. Plus (+) sign denotes a net luminal gain or efflux and a minus (−) sign a net luminal loss or influx.

* Significant difference from the basal period within the same chamber, $p < 0.001$.

† Significant difference from the basal period within the same chamber, $p < 0.01$.

NS = not significant.

mained higher though insignificantly so in the test chamber.

Ionic Fluxes

The results of the net fluxes of ions and fluid are summarized in Table 1. In this text influx denoted by a minus sign in front of the flux value means net luminal loss while efflux denoted by a plus sign means net luminal gain.

Sodium ion flux. In the test chamber immediately after misoprostol administration, there was a highly significant increase in Na^+ efflux into the lumen that was sustained until the end of the aspirin periods. Na^+ efflux returned to basal levels during the postaspirin periods (Fig. 5). In the control chamber during aspirin administration, there was a significant Na^+ influx from the lumen. This was reversed in the postaspirin periods, but the Na^+ efflux remained significantly less than that of the basal period.

Fluid flux across the mucosa behaved in exactly the same way as sodium in the test chamber (Fig. 6). In the control chamber, there was an insignificant fluid influx after the control period.

There were highly significant linear correlations between net changes in Na^+ and fluid in the test ($r = 0.9903$, $N = 18$, $p < 0.001$) and control ($r = 0.8652$, $N = 18$, $p < 0.001$) chambers.

Hydrogen ion flux. In the test chamber there was a significant ($p < 0.01$, t-test) H^+ efflux in the aspirin periods. In the control chamber there was no significant change in the net H^+ flux throughout the experiments. The only difference between the test and control

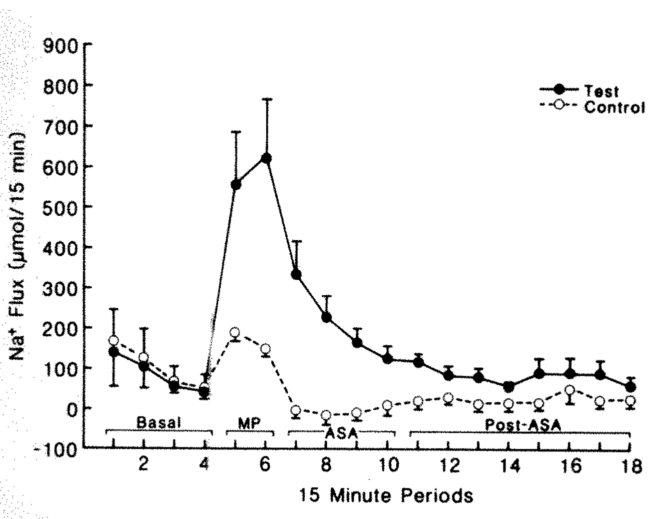


FIG. 5. The sequential changes in the flux of sodium in the test and control chambers during the basal, misoprostol/control, aspirin, and postaspirin periods.

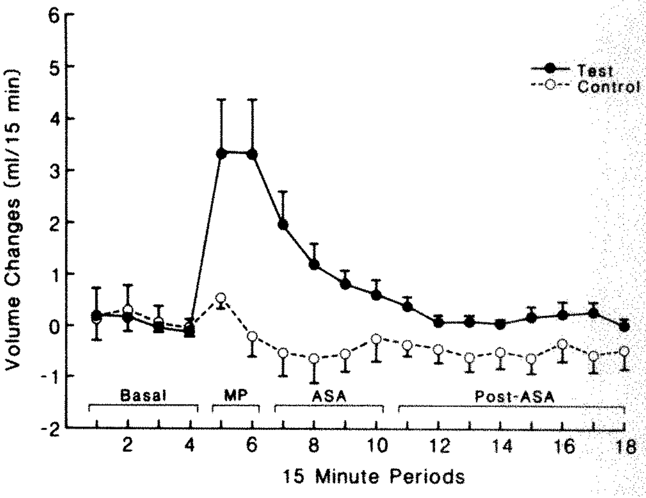


FIG. 6. The sequential changes in the flux of fluid in the test and control chambers during the basal, misoprostol/control, aspirin, and postaspirin periods. The pattern of the changes are identical to that of sodium.

chambers was a significantly higher H^+ influx in the latter in the postaspirin periods.

Relationship Between Gastric Mucosal Blood Flow and Fluxes

In the test chamber no correlations were observed between GMBF and the fluxes of Na^+, H^+, and fluid. In the control chamber, there were highly significant linear correlations between GMBF and fluid flux ($r = 0.7364$, $N = 18$, $p < 0.001$), and GMBF and Na^+ flux ($r = 0.5928$, $N = 18$, $p < 0.01$).

Discussion

Though the precise mechanism(s) of gastric cytoprotection is not known, some experimental evidence has emerged in support of the circulatory hypothesis.[1-6] According to the latter, an increase in GMBF is believed to (1) maintain an adequate supply of oxygen and nutrients to the mucosal cells, thereby preventing a deficit in energy metabolism; (2) supply bicarbonate that will buffer back-diffused hydrogen ions, and (3) rapidly eliminate both back-diffused hydrogen ions and the damaging agent that may have gained access into the subepithelial tissues.[35,36] Discrepancies in the results of previous studies on the role of GMBF in cytoprotection may be due to measurement techniques employed, experimental models, experimental designs, and route of administration of the PG.

HGC is a noninvasive method that has been validated for focal GMBF measurements in animals[37-39] and man.[37] Using this technique in our study after topical administration of misoprostol, we observed an immediate and small transient increase (18%) in focal GMBF. The nature of this increase in blood flow is suggestive of a direct vasodilatory effect by misoprostol. The results of this study differ from that of Leung et al.[27] who also (using HGC) reported no effect by misoprostol on resting GMBF and on GMBF during inhibition of stimulated acid secretion in rats. The differences may be due to the fact that in their study GMBF measurements were commenced 15 minutes after misoprostol treatment. Similar to our results, Sato et al.[31] reported that misoprostol increased gastric mucosal blood volume by 10–25% at various sites in the fundus and antrum as measured by reflectance spectrophotometry in healthy human male volunteers. Likewise, Larsen et al.[2] observed an increase in total gastric blood flow obtained by venous outflow in the canine chambered gastric segment model after topical misoprostol. Colton et al.[23] observed that misoprostol at doses that inhibited histamine-stimulated acid secretion reduced GMBF as measured by aminopyrine clearance, but the ratio (R) of GMBF to rate of acid secretion was actually increased. This indicated that misoprostol has a vasodilating effect in the gastric mucosal vascular bed. Similarly, intra-arterial PGE_1 has been reported to increase significantly total (by venous outflow and radioactive microspheres) and mucosal blood flow (by radioactive microspheres) in canine chambered gastric segment model.[40] Also, topical PGE_1 has been shown to dose-dependently increase superficial gastric mucosal microvascular flow measured by *in vivo* microscopy in rats.[41] The findings in this study confirm these earlier observations that misoprostol, a synthetic PGE_1 analog, is a vasodilator in the gastric mucosal vascular bed.

Our results also confirmed previous reports that misoprostol is cytoprotective.[2,24-26,28-30] The degree of mucosal swelling observed after misoprostol administration was surprising. The histology clearly attributed this gross observation to an edematous reaction within the lamina propria causing increased spacing and separation of the gastric glands. A thick mucoid layer overlying the surface epithelium was also evident in these sections. The aspirin-induced lesions were similar in severity and morphology to those described by other authors.[42] The frequent observation of a widened zone of lamina propria immediately below the surface epithelium is reminiscent of the fashion in which this layer is shed in response to necrotizing agents such as absolute ethanol.[43] The fact that many regions of tissue from the control chambers lacked any evidence of mucosal disruption could be attributed to the random nature of sample site selection as well as the length of the experimental period. It has been shown that epithelial repair under these conditions can begin within 3, and is completed within 60, minutes.[44]

The extent to which GMBF contributes to cytoprotection is unknown. Larsen et al, in the aforementioned study observed an increase in total gastric blood flow by misoprostol of over 400% that was sustained during subsequent aspirin-shock injury, and concluded that the increase in blood flow was responsible for the cytoprotective effects.[2] Recently, we have shown that topical aspirin induces a reduction in GMBF of varying degrees and that mucosal areas with blood flow reduced to below a *critical value* develop gross damage.[34] In this study we were unable to demonstrate that misoprostol pretreatment reverses aspirin-induced decrease in GMBF or maintains blood flow after aspirin administration. Our results therefore do not suggest that this transient vasoactive effect is an important mechanism of gastric cytoprotection.

In terms of ionic fluxes, Colton et al.[24] found no significant difference in the influx of H^+ and Cl^-, and efflux of Na^+ observed with misoprostol and aspirin when administered into canine Heidenhain pouches separately or together. They concluded that influx of H^+ and efflux of Na^+ from the stomach does not necessarily indicate mucosal damage. On the contrary, Larsen et al.[2] have reported that misoprostol had a negligible effect on the fluxes of Na^+, Cl^-, and H^+ that were not significantly different from the controls. In this study the only consistent flux changes observed were the significant increase in the efflux of Na^+ and fluid into the test chamber lumen immediately after administration of misoprostol. The efflux of Na^+ and fluid could be due to either damage to the gastric mucosal barrier by misoprostol, as was initially attributed to 16,16-dimethyl PGE_2,[45-47] or stimulation of a nonparietal cell secretion rich in Na^+.[48,49] Since no reports have shown that misoprostol damages the mucosa grossly or histologically, and the 200-μg dose of misoprostol used in this study has been experimentally and clinically shown to be cytoprotective, we favor the latter explanation for the observed increase in Na^+ and fluid efflux. The highly significant linear correlation observed in the test chamber between the fluxes of Na^+ and fluid further suggests that these fluxes may be mediated through the same pathway, namely, stimulation of nonparietal secretion rich in Na^+.

We cannot offer any explanation for the findings in H^+ fluxes. It is noteworthy that in the presence of PG, agents that stimulate active secretion of bicarbonate or Na^+-rich fluids,[50,51] disruption of the gastric mucosal barrier by topical damaging agents (*e.g.*, aspirin, alcohol, and bile salts) will not result in the classical picture proposed by Davenport, namely, back diffusion of H^+ and efflux of Na^+ into the lumen.[52] Neutralization of acid by bicarbonate and the large amounts of Na^+ effluxed into the lumen under these circumstances will inevitably alter the net ionic fluxes. This may be the reason for the failure to obtain results consistent with Davenport's hypothesis in this and other studies when an agent that stimulates active secretion of Na^+ bicarbonate is used. This finding also raises questions about the validity of using the efflux of Na^+ and the luminal loss of H^+ as indicators of gastric mucosal barrier damage under these circumstances. The linear relationship between GMBF and the fluxes of Na^+ and fluid in the control but not the test chamber may be accounted for by misoprostol since it is the only different variable between the two chambers.

In conclusion, though our results did show a significant and transient increase in GMBF by misoprostol pretreatment, it did not prevent subsequent decrease in GMBF by aspirin. The sustained efflux of Na^+-rich fluids (*i.e.*, nonparietal cell secretion) induced by this synthetic PGE_1 analog may be important in gastric cytoprotection. Our results confirm that misoprostol is vasodilatory and cytoprotective, and it stimulates nonparietal cell secretion. Further studies of the vasoactive effects of PG as an important mechanism of cytoprotection are required.

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Management of Stab Wounds to the Thoracoabdominal Region

A Clinical Approach

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We studied 324 patients admitted to Harlem Hospital Center from July 1981 to June 1986 with stab wounds of the thoracoabdominal region (area limited by a coronal circle through the fifth interspaces anteriorly and seventh interspaces posteriorly from above to a subcostal circle 5 cm caudad to the costal margins and 12th ribs from below). We divided this region into 12 zones (six symmetrical zones on each side) using the above upper and lower limits and the costal margins, the midlines, and the anterior and posterior axillary lines. This study was conducted to determine the incidence of transdiaphragmatic penetration for the thoracoabdominal region stab wounds in each of the 12 zones identified for the first time and applied in this study, and the reliability and safety of surgical management based mainly on physical examination. The highest incidence of transdiaphragmatic penetration occurred in stab wounds of the left anterior lower thoracic zone (21.7%). The lowest incidence was 0% and the overall incidence was 11%. Physical examination was accurate in making the diagnosis in 95.4% of all cases and no mortality was associated with a delay in diagnosis that may have resulted from the serial physical examinations. We conclude that this method of selective operative management based on physical examinations is accurate and safe.

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STAB WOUNDS of the chest can penetrate the abdomen across the diaphragm, and stab wounds of the abdomen can penetrate the chest. This propensity for thoracoabdominal or abdominothoracic penetration is mainly confined to an area we consider the thoracoabdominal region. This region is limited cephalad and caudad by a coronal circle running horizontally through the fifth interspaces anteriorly and the seventh interspaces posteriorly; the region is limited by another circle drawn 5 cm below and parallel to the costal margins and 12th ribs.

Management of many of the stab wounds of this region remains controversial, and mandatory laparotomy continues to be advocated by some.[1] The main reason for this controversy is the paucity of information on the true incidence of transdiaphragmatic penetration in wounds of this region and skepticism about the reliability of physical examination in diagnosing such injuries.

The purpose of this study was twofold: (1) to determine the incidence of transdiaphragmatic penetration (thoracoabdominal or abdominothoracic) for stab wounds of each of the 12 subdivisions of the thoracoabdominal region and if the incidence was high enough to justify mandatory laparotomy for any of the subdivisions; (2) to evaluate the accuracy of physical examination and the safety of selective operative management based on serial physical examinations.

Materials and Methods

We studied prospectively 324 patients with stab wounds of the thoracoabdominal region managed between July 1981 and June 1986.

There were 306 males and 18 females (M:F ratio: 11.5:1). The age ranged from 13 to 67, with an average of 31 years.

We divided the thoracoabdominal region into 12 zones using the costal margins, a circle drawn 5 cm caudad and parallel to the costal margins and 12th ribs, a coronal circle cephalad going across the fifth interspaces anteriorly and seventh interspaces posteriorly, the midlines, and the anterior and posterior axillary lines. The zones are anterior, lateral, and posterior lower thoracic and anterior, lateral and posterior subcostal on the right and the left (Figs. 1A and 1B).

All cases were examined to identify the exact location of the external wounds and analyzed based on the following objectives: (1) the incidence of thoracoabdomi-

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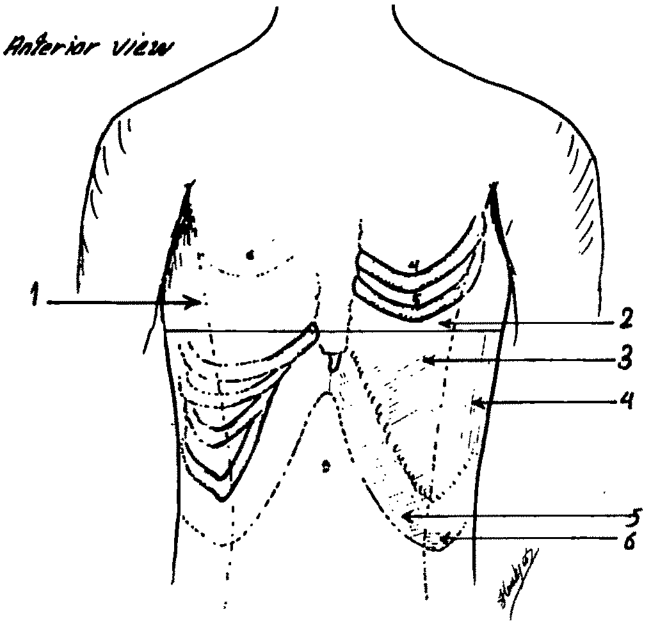

FIG. 1A. Landmarks, lines of division and zones of the thoracoabdominal region anterior view: 1. anterior axillary line, 2. fifth intercostal space, 3. anterior lower thoracic zone, 4. lateral lower thoracic zone, 5. anterior subcostal zone, and 6. lateral subcostal zone.

TABLE 1. *Incidence of Transdiaphragmatic Penetration for Stab Wounds of 12 Zones of Thoracoabdominal Region (Penetrating over Total Wounds and the Percentage)*

Zones	Lower Thoracic	Subcostal	Total
Right	4	3	7
Anterior	26	40	66
%	15.4	7.5	10.6
Left	10	5	15
Anterior	46	49	95
%	21.7	10.2	15.8
Right	4	0	4
Lateral	26	3	29
%	15.4	0	13.8
Left	8	0	8
Lateral	54	7	61
%	14.8	0	13.1
Right	1	0	1
Posterior	27	5	32
%	3.7	0	3.1
Left	1	0	1
Posterior	38	3	41
%	2.6	0	2.4
Total	9	3	12
Right side	79	48	127
%	11.4	6.25	9.4
Total	19	5	24
Left side	138	59	197
%	13.8	8.5	12.2
Total right and	28	8	36
left side	217	107	324
%	12.9	7.5	11.1

Note: the lower number of stab wounds and incidence of transdiaphragmatic penetration in the subcostal region compared to that of the lower thoracic; and the higher number of stab wounds of the left than that of the right side.

nal or abdominothoracic penetration (we use the term transdiaphragmatic penetration for both) for each of the 12 zones described; and (2) the degree of reliability of serial physical examinations and the safety of management assessed by the low negative laparotomy rate, and the low mortality and morbidity rates associated with operative surgical intervention made mainly by clinical evaluation.

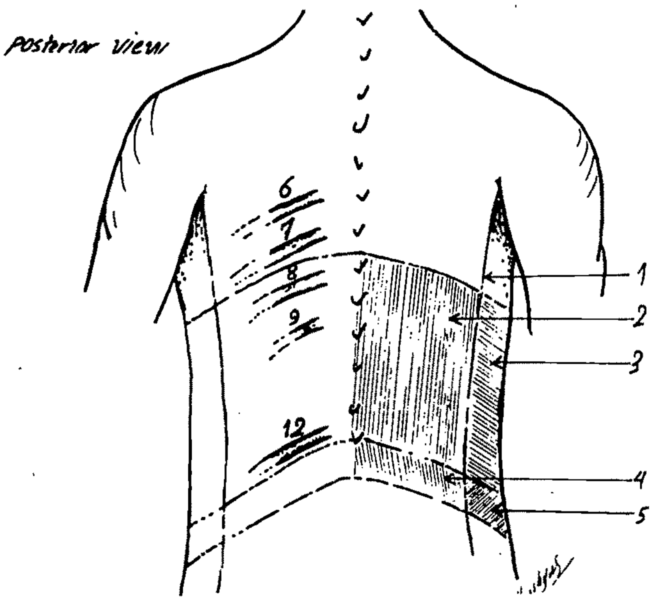

FIG. 1B. Landmarks, lines of division and zones of the thoracoabdominal region posterior view: 1. posterior axillary line, 2. posterior lower thoracic zone, 3. lateral lower thoracic zone, 4. posterior subcostal zone, and 5. lateral subcostal zone. Ribs 6–12 are outlined on the left.

Results

Thirty-six of the 56 patients managed by exploratory laparotomy among 324 patients admitted during the study period had transdiaphragmatic penetration (Table 1). Stab wounds of the left anterior lower thoracic zone were associated with the highest incidence of such transdiaphragmatic penetration (21.7%).

Analysis of the modes of diagnosis in the 36 patients with transdiaphragmatic penetration showed that in 26 cases, clinical findings alone were the main indication for the laparotomy at which diaphragmatic penetration was either confirmed (21 cases) or identified (five cases) (Table 2). One patient underwent emergency thoracotomy for hemorrhagic shock precluding clinical assessment of the abdomen for thoracoabdominal penetration. Nine patients (three with normal abdominal findings and six equivocal) were diagnosed with the aid of

TABLE 2. *Basis for Diagnosis in the 36 Cases with Stab Wounds of Thoracoabdominal Region and Transdiaphragmatic Penetration*

Means of Diagnosis	Number
Clinical findings alone	(26)*
Acute abdomen (lower thoracic wound)	11
Shock alone	2
Acute abdomen and shock (lower thoracic wound)	4
Omental evisceration through chest wall	4
Acute abdomen in subcostal wound; diaphragmatic injury detected at laparotomy	5
Clinical suspicion with ancillary confirmation	(6)*
Hematuria with confirmation of renal injury by I.V. pyelogram	2
Equivocal abdominal signs with positive peritoneal tap/lavage	4
Radiologic diagnosis in clinically benign abdomen	(3)*
Free subphrenic air, lower thoracic wound	1
Partial herniation of stomach in chest (5 weeks postinjury)	1
Free fluid in peritoneal cavity detected by abdominal ultrasonography	1
Incidental finding at operation	(1)*
Incidental finding of diaphragm injury at emergency thoracotomy for hemorrhagic shock	1
Total	36

* Totals for each category are given in parentheses.

TABLE 3. *Incidence of Negative Laparotomy among 56 Patients Managed by Laparotomy from 324 Patients with Stab Wounds in the Thoracoabdominal Region*

	Laparotomies	All Patients
Stab wounds of the subcostal area	2/25	2/107
%	8	1.87
Stab wounds of the lower chest	3/31	3/217
%	9.6	1.54
All stab wounds of the thoracoabdominal region	5/56	5/324
%	8.9	1.85

plain x-ray films, IVP, ultrasonography, and peritoneal tap/lavage.

Table 3 shows the incidence of negative laparotomy among the 56 patients who underwent exploratory laparotomy. Twenty-five had subcostal wounds and eight of them had diaphragmatic injuries. Of the 25 patients, 23 had significant intra-abdominal injuries. Thirty-one patients had stab wounds of the lower chest. Two among the patients with subcostal wounds and three among the patients with lower thoracic wounds had negative laparotomies. The remaining 268 patients were managed nonoperatively.

In 15 patients with lower thoracic stab wounds, including one with transdiaphragmatic penetration, clinical evaluation of the abdomen was precluded by the need for emergency thoracotomy. Excluding these patients from the 324 leaves 309 patients evaluated by serial physical examinations. Accurate clinical evaluation was achieved in 295 of the 309 (95.5%) [193 of 202 with lower thoracic wounds (95.5%) and 102 of 107 with subcostal wounds (95.3%)]. Six patients had equivocal findings on abdominal examination, which prompted ancillary investigative measures (tap/lavage in four and IVP in two). Physical examination was falsely negative in three patients with transdiaphragmatic penetration

TABLE 4. *Injuries and Causes of Death in 11 Cases among 324 Patients with Stab Wounds of the Thoracoabdominal Region*

Patient No.	Age (yr)	Sex	Injuries	Cause of Death	Place or Time of Death
1	62	M	Aorta, IVC, renal vein, stomach, colon, and diaphragm	Exsanguination	OR
2	50	M	Portal vein, liver, hepatic artery, and diaphragm	Exsanguination	OR
3	44	M	Liver-hepatic vein	Exsanguination	OR
4	47	M	Pulmonary vein, and artery	Exsanguination	OR
5	52	M	Heart, pulmonary vessels	Exsanguination	OR
6	59	M	Superior vena cava	Exsanguination	ER, DOA
7	25	M	Inferior vena cava and liver	Exsanguination	ER, DOA
8	50	M	Inferior vena cava, hepatic artery, and portal vein	Exsanguination	ER, DOA
9	40	M	Heart	Exsanguination	ER, DOA
10	32	M	Duodenum and kidney	Sepsis and DIC	2 weeks after operation
11	16	M	Stomach, jejunum, and concomitant carotid artery injury	Cerebral anoxia from carotid artery injury	2 weeks after operation

ER = emergency room.
OR = operating room.
DOA = dead on arrival.
IVC = inferior vena cava.

TABLE 5. *Morbidity among 324 Cases of Stab Wounds in the Thoracoabdominal Region*

Patient No.	Age (yr)	Sex	Type of Complication	Location of Stab Wound	Internal Injuries	Delay in Diagnosis
Chest complications						
1	31	M	Empyema	Thoracic	Spleen, diaphragm, and gastric protrusion	None
2	64	M	Empyema	Thoracic	Hemothorax treated by chest tube	None
3	22	M	Atelectasis	Thoracic	Liver and diaphragm	None
4	31	M	Prolonged air leak	Thoracic	Heart and lung	None
5	38	F	Clotted hemothorax	Thoracic	Pericardial laceration and hemothorax treated initially by chest tube, followed by thoracotomy for decortication	None
6	29	M	ARDS	Thoracic	Hemothorax treated by chest tube	None
7	26	M	Atelectasis	Subcostal	Liver and stomach	None
8	31	M	Lung abscess	Subcostal	Diaphragm with partial gastric herniation	5 weeks
Intra-abdominal complications						
9	26	M	Small bowel obstruction	Subcostal	Liver and stomach	None
10	26	M	Small bowel obstruction	Subcostal	Liver and colon	None
11	53	M	Small bowel obstruction	Thoracic	Heart, negative laparotomy	None
Wound complications						
12	38	F	Infection	Thoracic	Pericardial laceration and hemothorax treated initially by chest tube, followed by thoracotomy for decortication	None
13	32	M	Infection	Subcostal	Liver and diaphragm	None
Cardiac and vascular complications						
14	26	M	Ventricular septal defect	Thoracic	Heart	None
15	38	M	Superior vena caval thrombosis (secondary to subclavian cannulation)	Thoracic	Liver, spleen, and diaphragm	None

(Table 2). In five patients physical examinations were falsely positive resulting in negative laparotomies (Table 3).

Mortalities among the 324 patients admitted with stab wounds of the thoracoabdominal region are listed in Table 4. There were 11 deaths with an overall mortality rate of 3.4%. Four cases were classified as dead on arrival, after emergency thoracotomy was performed for open chest cardiac compression and resuscitation efforts based on possible signs of life. Excluding the four cases of dead on arrival, the mortality rate would be 2.2%. Five were in profound shock upon arrival to the emergency room from exsanguinating cardiac or major vascular injuries. One died of cerebral ischemia resulting from a concomitant carotid artery injury, and one died of sepsis, both 2 weeks after operation. The average age for the mortality group was 43.36 years. Delay in diagnosis was not associated with mortality in any instance.

Table 5 shows the morbidity rate for this series. There were 15 complications in 14 patients. Delay in diagnosis was associated with morbidity in one case; this was a patient with an epigastric stab wound who was observed for 4 days and then discharged asymptomatic only to return 5 weeks later with partial herniation of the stomach into the chest. Following transthoracic repair of his diaphragm he developed a lung abscess. Delay in making the diagnosis up to 18 hours from the time of injury occurred in four other patients, but it was not associated with morbidity.

There were six cases of visceral herniation through the diaphragm to outside. The herniating viscera were stomach in two cases and omentum in the other four.

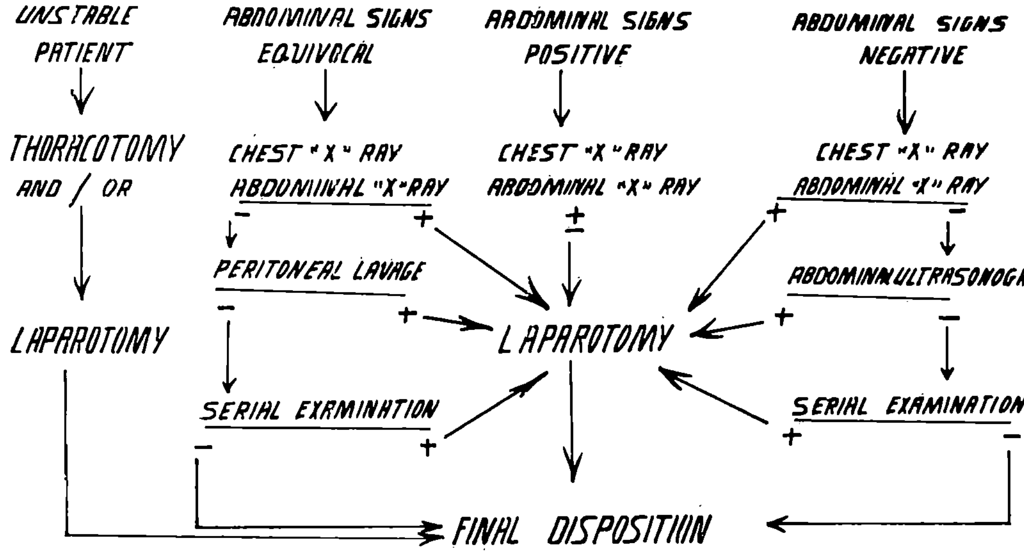

FIG. 2. Our algorithm for management of patients with stab wounds of the thoracoabdominal region.

There were 16 hepatic, 8 splenic, 5 gastric, 4 colonic, 4 renal, and 2 major vascular associated injuries in the 36 cases with transdiaphragmatic penetration. In seven cases diaphragmatic injury was the only visceral injury.

Discussion

In stab wounds of the thoracoabdominal region, mortality and morbidity rates are mainly dependent on concomitant injuries to thoracic and abdominal organs sustained directly or transdiaphragmatically. The diaphragmatic injury per se is not a major factor in development of complications early on, but it can cause delayed morbidity and even mortality.

Optimal and timely management should prevent avoidable mortality and morbidity without excessive use of costly and risk-laden, diagnostic procedures. Mandatory laparotomy for all penetrating wounds of the abdomen and lower chest has been advocated on the grounds that it is the only sure way of making an early diagnosis of transdiaphragmatic penetration.[1–3] But in the only report we could find addressing the incidence of transdiaphragmatic penetration for lower thoracic stab wounds, Moore et al.[4] have indicated an incidence of 15%. Obviously with this incidence mandatory laparotomy would result in a large number of unnecessary operations. Even among patients subjected to laparotomy, missed diaphragm injuries have been reported.[1,5,6] Furthermore, negative laparotomy is not an innocuous procedure with reported mortality rates ranging from 0–6.3%[7–9] and morbidity rates of 17–19%.[9,10] Therefore, mandatory laparotomy is not a satisfactory method of management.

Since Shaftan's report[11] selective operative management has become the prevalent approach to stab wounds of the abdomen and lower chest. Serial physical examinations have been suggested as the basis for selection.[12,13] Lee et al.[13] found serial physical examinations to be reliable in 88.6% with a negative laparotomy rate of 7.8%. Others have found physical examination less reliable and sought to use ancillary measures to arrive at an earlier diagnosis.

Local exploration of the wound may be a useful screening measure for abdominal stab wounds, but its use in chest wounds is less informative and it may also induce pneumothorax. Peritoneal lavage is the most popular ancillary measure, and its application has been championed in several series.[14,15] Using lavage Thal[14] in 213 out of 412 patients with abdominal and lower thoracic stab wounds had nine negative laparotomies among 412 patients; the false-negative lavage rate was 4.2%.

Feliciano et al.[15] in the largest series of peritoneal lavages for abdominal stab wounds reported a 91.2% accuracy for lavage in patients with peritoneal penetration but no abdominal sign. However, there were 37 negative laparotomies performed per year during the 4 years duration of the study, making the negative laparotomy rate for the 1150 patients with abdominal penetration 12.86%. Also, the value of peritoneal lavage in diagnosing diaphragmatic injury is challenged.[16] Thoracoscopy[17] and peritoneoscopy[18] have been advocated as methods of selection of patients for operative intervention, but they are cumbersome and have not been adopted on any large scale.

At Harlem Hospital Center, serial physical examinations have been the basis of selective operative management for stab wounds of the abdomen and lower chest during the last 10 years. In reviewing the cases managed during July 1981 through June 1986 we found that all of the diaphragmatic injuries due to stab wounds and 95% of those due to gunshot wounds fell within the boundaries of the region we have outlined as the thoracoabdominal region. The incidence of transdiaphragmatic injury for stab wounds of this region was 11.1%. We subdivided the region into 12 zones to see if the incidence for any one zone was high enough to justify mandatory laparotomy. The highest rate of transdiaphragmatic injury was found in wounds of the left anterior lower thoracic zone (21.7%), but even this incidence is too low to justify mandatory laparotomy. For the entire lower thorax stab wounds, transdiaphragmatic penetration rate in this series was 12.9%. Physical examination was accurate in selecting appropriate methods of management in 95.5% of patients. We used peritoneal lavage only in equivocal cases and in those with an altered sensorium. Our recent experience with ultrasonography has encouraged us to include it in our algorithm (Fig. 2) for managing wounds of the thoracoabdominal region. Delay in making the diagnosis based on physical examinations was not associated with mortality. Among the 56 patients managed by laparotomies five (8.9%) tested negative. The overall negative laparotomy rate for all patients with stab wounds of the thoracoabdominal region was 1.54%.

Although the true incidence of transdiaphragmatic injury in stab wounds of the thoracoabdominal region can only be determined by meticulous mandatory laparotomy, the results of this study suggest that selective laparotomy based on serial physical examinations supplemented by the judicious use of ancillary measures when necessary is an accurate and safe method of diagnosis and management of thoracoabdominal stab wounds.

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Microbial Colonization of Tumors in Relation to the Upper Gastrointestinal Tract in Patients with Gastric Carcinoma

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The microbial colonization of the oropharynx, the esophagus, the stomach, and the duodenum was studied in relation to the microbial flora found on tumor and gastric mucosal biopsies in 23 patients with gastric carcinoma. The tumor was colonized in all patients, and the stomach, the esophagus, the duodenum, and the gastric mucosa were colonized in 96%, 87%, 83%, and 78% of the patients, respectively. The most common microorganisms isolated were *streptococci, bifidobacteria, lactobacilli,* and *Bacteroides* species, belonging to the normal oropharyngeal flora. Microbial colonization with gram-negative rods, *Clostridium* species or yeasts, was present in at least one site in 91% of the patients. *Clostridium* species were isolated from 57% of the patients. The total numbers of microorganisms recovered from the tumor biopsies did not vary with the intraluminal gastric pH. A relation between the gastric pH and the total number of microorganisms in the gastric juice existed. Significant higher numbers of different strains of microorganisms ($p < 0.005$) colonized the tumor compared to the gastric mucosa. Anaerobic microorganisms colonized the tumor significantly more often than the mucosa ($p < 0.001$). Antibiotic agents used as prophylaxis in gastric cancer surgery should cover both aerobic and anaerobic microorganisms, including *B. fragilis.*

PATIENTS with gastric carcinoma undergoing surgery are at high risk of developing postoperative infectious complications. The risk of infection is related to the density of the microbial colonization of the stomach, and the microorganisms causing infections are usually present in the stomach at the time of operation.[1,2]

The luminal floras of the oropharynx, the esophagus and the stomach, have previously been studied in patients with different diseases of the stomach by Sjöstedt et al. (Table 1).[3] Patients with gastritis, a history of previous gastric resection, and gastric carcinoma were found to have the highest pH of the gastric fluid and also to harbor more microorganisms in the stomach. Patients with gastric carcinoma were found to harbor the largest numbers of different microbial species and also more species not belonging to the normal oropharyngeal microflora than patients with any other gastric diseases. Patients with gastric carcinoma are almost invariably colonized in the stomach with microorganisms derived from the normal oropharyngeal flora but also often with enteric gram-negatives and yeasts. These patients have also been found to harbor anaerobes such as *Clostridium* species and *Bacteroides* species, including *B. fragilis,* in the stomach.[1-4]

In previous reports the microflora has been studied by means of aspiration of the intraluminal content. In this study not only the luminal flora of the oropharynx, the esophagus, the stomach, and the duodenum were studied, but also the microbial colonization of the tumor itself, which was compared with the normal gastric mucosa in patients with carcinoma of the stomach.

Materials and Methods

Twenty-three patients, 20 men and 3 females (mean age: 68.5 years) were studied. They all had histologically verified gastric carcinoma diagnosed at an earlier endoscopy. The samples for microbiologic analysis were obtained during an endoscopy performed as a part of the preoperative evaluation of the patient.

Before endoscopy, mixed saliva samples of 1 mL were collected by the patient spitting into a sterile glass tube.

Samples of 1 mL of fluid from the esophagus, the stomach, and the duodenum were collected during endoscopy by means of aspiration through a sterile polyethylene tube introduced into the biopsy channel of the

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TABLE 1. *Numbers of Microorganisms Isolated from the Upper Gastrointestinal Tract in Patients Without Gastric Disease*[3]

Microorganisms	Log Numbers of Microorganisms/mL: Oropharynx	Esophagus	Stomach
Aerobic species			
Micrococci, staphylococci	9×10^7	0	$<10^2$
Hemophilus neisseria	9.7×10^6	0	$<10^2$
Streptococci	7.4×10^7	$<10^3$	$<10^2$
Anaerobic species			
Bifidobacteria lactobacilli	3.1×10^6	$<10^2$	$<10^3$
Veillonella	3.3×10^7	$<10^2$	$<10^3$
Fusobacteria	6.5×10^5	0	0
Bacteroides	2.2×10^7	$<10^3$	$<10^3$

endoscope. To prevent contamination a new sterile tube was placed in the biopsy channel each time the endoscope was moved to a new site. In the esophagus and the duodenum 1 mL of sterile saline (0.9%) was first injected into the lumen and then aspirated, and by this technique a luminal washing was obtained. In the stomach it was always possible to collect 1 mL of gastric fluid without a luminal washing.

After all luminal samples had been obtained the tumor was located. Three biopsies from the visually unaffected mucosa as far away as possible from the tumor were obtained and placed in three glass tubes with sterile saline. With a new pair of biopsy-forceps three biopsies from the tumor were then taken and placed in three glass tubes with sterile saline. All samples were immediately transported to the laboratory and processed.

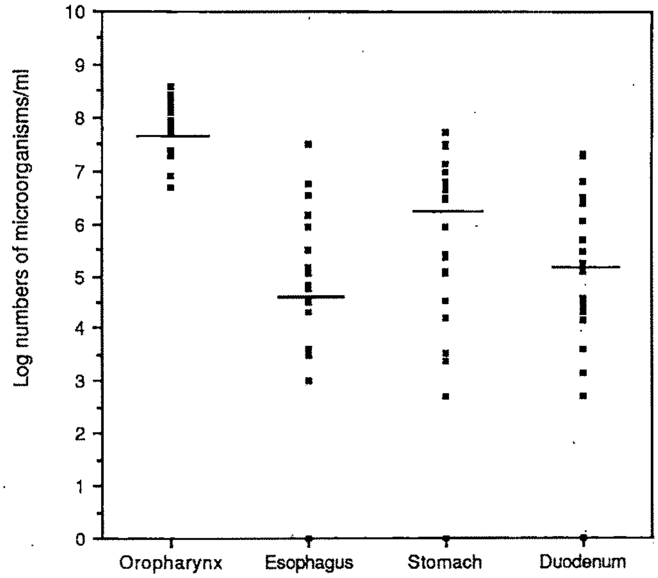

FIG. 1. Total numbers of microorganisms isolated from the oropharynx, esophagus, stomach, and duodenum in 23 patients with gastric carcinoma.

The samples of saliva, esophageal washings, gastric fluid, and duodenal washings were suspended in prereduced peptone yeast extract medium. They were diluted, inoculated on nonselective and selective media and manipulated as described by Heimdahl and Nord.[5]

The biopsies from the first 11 consecutive patients were cut into small pieces, homogenized, and then suspended in 4.5 mL prereduced peptone-yeast extract medium. Aliquots of 0.1 mL were then inoculated on selective and nonselective media.

In the other 12 consecutive patients a quantitation of the microflora isolated from the biopsies was also made. These biopsies were first weighed and then cut into small pieces, homogenized, and suspended in prereduced peptone-yeast extract medium. Tenfold serial dilutions were prepared to 10^{-4}. Each dilution was inoculated on nonselective and selective media.

The aerobic agar plates were incubated for 24 hours (luminal samples) or 48 hours (tissue samples) at 37 C, and the anaerobic agar plates for 2 days (luminal samples) or four days (tissue samples) at 37 C in an anaerobic chamber (Forma Scientific®, Marietta, OH).

Aerobic bacteria were identified as described by Heimdahl and Nord,[5] and anaerobic bacteria were identified using biochemical tests and gas-liquid chromatography.[6]

The pH of 4 mL of aspirated gastric juice was estimated using a pH-Meter 29 (Radiometer®, Copenhagen).

Statistical methods used were paired *t*-test and Fisher's exact test.

Results

Oropharynx

All patients harbored normal numbers (Table 1) of aerobic bacteria such as *streptococci, micrococci/staphylococci*, and *hemophilus/neisseria* and anerobic bacteria such as *bifidobacteria/lactobacilli, veillonella, fusobacteria*, and *bacteroides*. The median total counts of microorganisms were 7.0×10^7/mL (Fig. 1). Microorganisms not belonging to the indigenous oropharyngeal flora were colonizing 17/23 (73.9%) of the patients. *Clostridium* species were found in 39.1%, gram-negative aerobic rods in 30.4%, and yeasts in 21.7% of the patients (Tables 2 and 3).

Esophagus

The total counts of microorganisms were lower than in the oropharynx (median: 6.0×10^4 microorganisms/mL) (Fig. 1). Colonization of the esophagus was found in 20/23 (87%) of the patients. *Streptococci* were found in 87%, *micrococci/staphylococci* in 60.9%, and *bifido-*

TABLE 2. *Colonization with Microorganisms not Belonging to the Indigenous Oropharyngeal Microflora in 23 Patients with Gastric Cancer*

	No. of Patients Colonized					
Organisms	Oral Cavity	Esophagus	Stomach	Duodenum	Mucosa	Tumor
Streptococcus fecalis	1	1	1	1	1	1
Escherischia coli	1	—	2	3	—	—
Klebsiella pneumoniae	1	—	3	2	1	1
Klebsiella ozaenae	1	—	—	—	—	—
Enterobacter cloace	2	—	1	—	—	—
Proteus morganii	—	—	1	1	1	1
Pseudomonas maltophila	1	—	1	—	—	—
Serratia species	1	—	—	—	—	—
Hafnia alvei	—	—	—	1	—	—
Nonidentified*	—	—	—	—	—	—
Gram-negative rods	—	—	—	—	—	1
Clostridium perfringens	—	—	2	2	—	2
Clostridium species	9	3	3	5	—	4
Candida albicans	2	2	3	3	1	1
Torulopsis glabrata	2	—	—	—	—	1
Torulopsis candida	1	—	—	—	—	—

* Nonidentified gram-negative rods colonized the tumor in one patient.

bacteria/lactobacilli in 52.2% of the patients. Aerobic gram-negative rods did not colonize the esophagus, but *Clostridium* species were found in 13%, yeasts in 8.7%, and *enterococci* in 4.3% of the patients (Tables 2 and 3).

Stomach

The luminal gastric flora had a higher concentration of microorganisms (median total counts of microorganisms: 3.0×10^6/mL) than the esophageal flora but not as high as the oropharyngeal flora (Fig. 1). Twenty-two (95.7%) of the patients harbored microorganisms in the gastric juice. There was a clear correlation between the total numbers of microorganisms and the pH of the gastric juice (Fig. 2). *Streptococci* were found in 87%, *bifidobacteria/lactobacilli* in 78.3%, and *micrococci/staphylococci* in 60.9% of the patients. Microorganisms not belonging to the normal oropharyngeal microflora were found in 11/23 (47.8%) of the patients. *Clostridium* species were found in 21.7%, aerobic gram-negatives rods in 21.7%, yeasts in 13.0%, and *enterococci* in 4.3% of the patients (Tables 2 and 3). In only two patients did these microorganisms also colonize the oropharynx.

Duodenum

The median total counts of microorganisms were 1.0×10^5/mL (Fig. 1). Microbial colonization was found in 19/23 (82.6%) of the patients. *Bifidobacteria/lactobacilli* were found in 65.2%, *streptococci* in 60.9%, and *veillonella* in 43.5% of the patients. Microorganisms not belonging to the normal oropharyngeal flora were found in 11/23 (47.8%) of the patients. *Clostridium* species colonized 30.4%, aerobic gram-negative rods 17.4%, yeasts 13.0%, and *enterococci* 4.3% of the patients (Tables 2 and 3).

TABLE 3. *Microbial Colonization of the Upper Gastrointestinal Tract, Gastric Mucosa, and Tumor in 23 Patients with Gastric Carcinoma*

	Oropharynx	Esophagus	Stomach	Duodenum	Mucosa	Tumor	At Least 1 Site Colonized
Micrococci/staphylococci	*	60.9	60.9	34.8	43.5	73.9	82.6
Streptococci/other gram-positive cocci	*	87	87	60.9	60.9	91.3	100
Hemophilus/Neisseria	*	39.1	30.4	30.4	13	13	60.9
Enterococci	4.3	4.3	4.3	4.3	—	4.3	8.7
Enteric gram-negative microorganisms	12.7	—	17.4	17.4	4.3	8.7	34.8
Bifidobacteria/Lactobacilli	*	52.2	78.3	65.2	13	47.8	95.7
Veionella	*	34.8	43.5	43.5	13	17.4	78.3
Fusobacteria/leptotrichia	*	21.7	47.8	26.1	—	—	60.9
Bacteroides	*	39.1	43.5	34.8	—	26.1	73.9
Clostridium species	39.1	13.0	21.7	30.4	—	26.1	56.5
Yeasts	21.7	8.7	13.0	13.0	4.3	4.3	30.4
Total % of patients colonized	73.9	87	95.7	82.6	78.3	100	—

* Normal oropharyngeal flora.

Values are given as % of patients colonized.

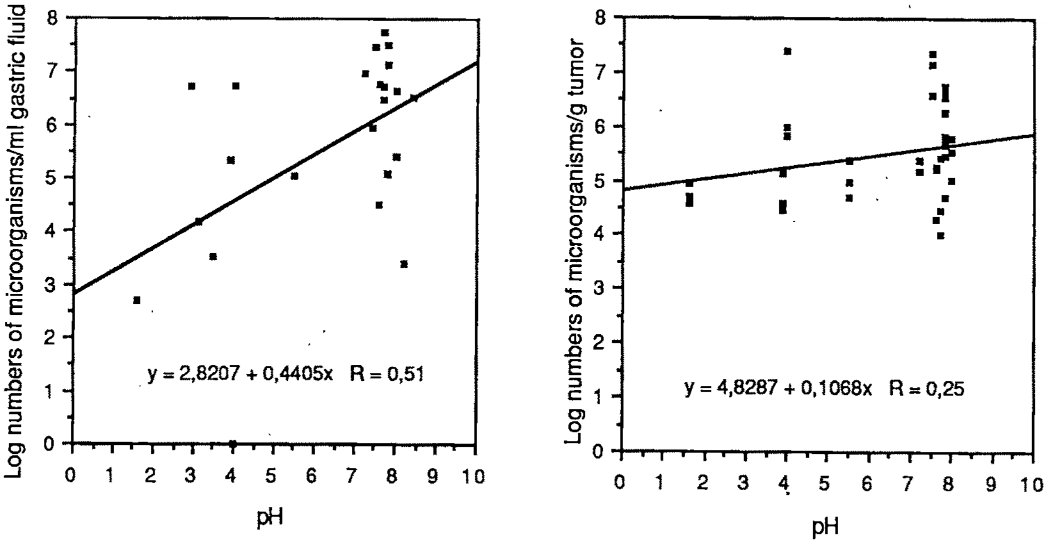

FIG. 2. (*left*) Relationship between total viable counts of microorganisms/mL gastric juice and gastric pH in 23 patients with gastric carcinoma. A significant correlation (r = 0.51) was found between increase in pH and numbers of microorganisms. The equation of the regression line is shown in the figure. (*right*) Relationship between total viable counts of microorganisms/g tumor tissue and gastric juice pH in 36 tumor biopsies from 12 patients with gastric carcinoma. No significant correlation was found (r = 0.25). The equation of the regression line is shown in the figure.

Gastric Mucosal Biopsies

Eighteen (78.3%) of the patients were colonized on the mucosal biopsies, and 17/23 (73.9%) had growth of aerobic microorganisms, and 7/23 (30.4%) had growth of anaerobic microorganisms. *Streptococci* (in 60.9% of the patients) and *micrococci/staphylococci* (in 43.3% of the patients) were the most common findings. Aerobic gram-negative rods were found in one patient (4.3%) and yeasts were found in another patient (4.3%). None of the patients was colonized with *Clostridium* species on the normal mucosa (Tables 2 and 3). The mean number of different strains was 2.9 on the mucosal biopsies (Table 4, Fig. 3).

Tumor Biopsies

All patients were colonized on the tumor and 22/23 (95.7%) had growth of aerobes and 20/23 (87%) had growth of anaerobes. Anaerobic bacteria colonized the tumor significantly ($p < 0.001$) more often than they did the normal mucosa (Table 4). *Clostridium* species were found on the tumor in 26.9% of the patients, significantly ($p < 0.05$) more often than on the normal mucosa. *Streptococci* (in 60.9% of the patients) and *micrococci/staphylococci* (in 43.3% of the patients) were the most common findings (Tables 2 and 3). Ten (43.5%) of the patients were colonized with microorganisms not belonging to the normal oropharyngeal microflora. Aerobic gram-negative rods were found in 8.7% and yeasts in 4.3% of the patients. The mean number of different strains was 6.5 on the tumor biopsies, which was significantly ($p < 0.0005$) more than on the mucosal biopsies (Table 4, Fig. 3). The total counts of microorganisms on the tumor biopsies from patients with a pH of 4 or less did not differ from the patients with a higher pH (Fig. 2). The total numbers of microorganisms were 2–30 times higher on the tumor samples than on the mucosa samples in all but one patient.

TABLE 4. *Comparison Between Microbiologic Findings from Mucosal and Tumor Biopsies in 23 Patients with Gastric Carcinoma*

	Mucosa	Tumor	P Value
No. of patients colonized	18	23	$p < 0.05$*
Aerobes	17	22	NS
Anaerobes	7	20	$p < 0.001$*
Gram-negative rods	1	2	NS
Clostridium species	0	6	$p < 0.05$*
Bacteroides	0	6	$p < 0.05$*
Yeasts	1	1	NS
Mean No. of strains	2.9	6.5	$p < 0.0005$†
Aerobic strains	2.4	4.2	$p < 0.0005$†
Anaerobic strains	0.7	2.4	$p < 0.0005$†

* Fischer's exact test.
† Paired t-test.

Discussion

In this study, the microbial colonization of the oropharynx, the esophagus, the stomach, and the duodenum was compared with the colonization of the tumor and the gastric mucosa in patients with gastric carcinoma.

We have previously reported on the intraluminal flora of the upper gastrointestinal tract in patients with different gastric diseases including carcinoma.[3] The oropharynx of patients with carcinoma are colonized with gram-negative rods, *Clostridium* species, and yeasts. This is probably not due to their gastric disease because the same microbial colonization in patients with other gastric diseases and even in normal subjects was found.[3] *Clostridium* species, however, were only found in patients with carcinoma.

In the esophagus, the concentration of microorganisms was much lower than in the oropharynx. This can only in part be explained by the sampling procedure because the dilution of the esophageal fluid with 1 mL of saline cannot explain the fall in concentration from 10^7 microorganisms/mL in the oropharynx to 10^4 microorganisms/mL in the esophagus. Other factors influencing the density of the esophageal flora can be the peristalsis of the esophagus causing a rapid washout of the microbes, secretion from the mucosa resulting in a dilution with less ability for microbial attachment or local immunologic factors. It is noteworthy that gram-negative rods in no case were isolated from the esophagus whereas *Clostridium* species and yeasts were, which is in accordance with our previous findings.[3]

Reports of the findings of microorganisms in preoperative and peroperative gastric aspirates have been published. In an earlier study it was found that patients with gastric carcinoma have higher bacterial counts and are colonized with higher numbers of different species than patients with other gastric diseases.[3] Gatehouse et al.[1] found growth of microorganisms in preoperative gastric aspirates in all of 35 patients investigated, and 54% of these patients had a total viable count greater than 5 × 10^6 organisms/mL, which is in an accordance with our findings. Muscraft et al.[4] investigated 31 patients with gastric carcinoma and compared them with patients with intact stomach receiving cimetidine and patients with resected stomachs. They found that *E. coli* (in 51% of the patients) and *Clostridium* species (in 25.8% of the patients) were more common in the carcinoma group. They also reported high frequencies of *Streptococcus fecalis* (70.9%) and *B. fragilis* (38.7%). In the present investigation these frequencies of *E. coli, S. fecalis,* or *B. fragilis* were not found, but a comparable frequency of *Clostridium* species of 21.7% and a frequency of *Bacteroides* species of 43.5% in the gastric aspirates were found.

The duodenal flora has not previously been studied in patients with gastric carcinoma. Normally, there is no permanent flora in the duodenum, but subjects with achlorhydria may be colonized with low numbers of microorganisms (median 10^3 microorganisms/mL). *Enterococci,* aerobic gram-negatives, oral aerobes and anaerobes and yeasts but not *Clostridium* species have been recovered.[7] We found a colonization in 82.6% of the patients and a median count of 1.0 × 10^5 microorganisms/mL; *Clostridium* species were found in 30.4% of the patients with gastric carcinoma.

No correlation between the colonization of the different sites of the gastrointestinal tract was found. For example, of the 11 patients colonized in the gastric aspirates with aerobic gram-negative rods, *Clostridium* species or yeasts, only two were colonized with the same microorganisms in the oropharynx.

It is generally agreed that there exists a relationship between the pH of the gastric fluid and the numbers of microorganisms in the gastric fluid.[3,4,8,9] Gastric aspirates with a pH of 4 or less are usually sterile. In this study, the colonization of the tumors, however, did not seem to be dependent of the pH of the gastric fluid. All patients with a pH of 4 or less were colonized on the tumor surface, and the total numbers of microorganisms did not differ significantly from the total numbers found on the tumors from patients with a higher pH. Consequently, the tumor may act as a reservoir on which the microorganisms may be protected from the acidity of the gastric juice and thus give rise to a continuous release of microorganisms into the gastric lumen. There were no significant differences between the species found in the intraluminal flora and the species found on the tumors.

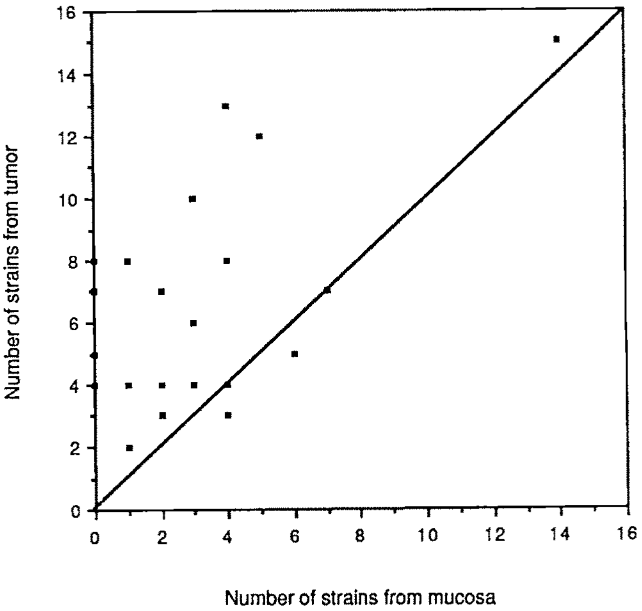

FIG. 3. The number of different predominant strains of microorganisms isolated from gastric mucosal biopsies in relation to the number of different strains isolated from tumor biopsies in 23 patients with gastric carcinoma. Points situated above the diagonal line indicate patients with a larger number of predominant strains on the tumor than on the mucosa. Points below the diagonal line indicate patients with a larger number of strains on the mucosa than on the tumor.

Some significant differences were found between the colonization of the mucosa and the tumors. Microorganisms were found in higher numbers on the tumors in all but one patient. Growth of microorganisms were found on tumor biopsies from all patients whereas the mucosa showed no growth at all in five patients. The numbers of different strains isolated from the tumor biopsies were significantly higher than the numbers of strains found on biopsies from the mucosa. Anaerobes seemed to have a strong tendency to grow on the tumors; *Bacteroides* species and *Clostridium* species could only be isolated from the tumors. The fact that the biopsies from the normal mucosa showed some colonization in most patients is surprising, but one explanation is that elderly patients often have various degrees of gastritis and that a damaged mucosa is more likely to be colonized.[10,11]

Clostridium species, including *C. perfringens,* seems to be the microorganisms, not belonging to the normal oropharyngeal flora, that are most likely to colonize the upper gastrointestinal tract of patients with gastric carcinoma. *Clostridium* species have in other studies been found to colonize patients with carcinoma of the colon[12] and patients undergoing bone marrow transplantation.[13] Overgrowth or colonization with *Clostridium* species may therefore in some way be associated with malignant disease.

Patients with gastric carcinoma are heavily colonized in the upper gastrointestinal tract, and microorganisms not belonging to the normal oropharyngeal flora can be found in most of the patients. These patients are at high risk of developing postoperative infectious complications, and previous reports have shown frequencies of between 13% and 56%.[1,15,16]

Cephalosporins have been recommended as antibiotic prophylaxis in gastric surgery since the study of Polk and Lopez-Mayor in 1969[17] and others.[18-23] In well-controlled studies, cephalosporins have been shown to significantly reduce the number of postoperative infections after gastric surgery. Stone et al.[19] used cefazolin and reduced the rate of postoperative infections from 22% to 4%. However, there is no study dealing specifically with prophylaxis in patients with gastric carcinoma. All studies include patients with various gastric diseases, and the number of patients with gastric carcinoma are often not stated. Keighley et al.[24] have reported on selective antibiotic prophylaxis in gastric surgery, including patients with gastric carcinoma. Only patients with total viable counts of $>10^6$ microorganisms/mL were given antibiotics. The choice of antibiotics was guided by the preoperative culture. The patients received ampicillin, gentamicin, clindamycin, or combinations of these agents. Full anaerobic coverage was judged to be appropriate in 10.5% of the patients receiving prophylaxis. Although this model of selective use of antibiotic prophylaxis was successful with an infection rate of 8%, it appears to be impractical. In the choice of antimicrobial agents for prophylaxis, simpler guidelines are needed.

Streptococci, staphylococci, enterococci, enterobacteria, Bacteroides species, including *B. fragilis,* and *Clostridium* species have been isolated from gastric aspirates in patients with gastric carcinoma. These microorganisms have also been isolated from postoperative infections after gastric surgery.[1-4,14-16,19,21] The present study has shown that in patients with gastric carcinoma the tumor itself is always colonized, often with anaerobic microorganisms, including *Bacteroides* species and *Clostridium* species.

From the present study and also from other studies it may be concluded that antimicrobial agents covering both aerobic and anaerobic bacteria, including *B. fragilis,* should be used as antibiotic prophylaxis in patients with gastric carcinoma undergoing surgery.

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Results of Salvage Surgery for Mammary Recurrence Following Breast-conserving Therapy

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A retrospective analysis was performed of 118 surgically treated mammary recurrences, occurring following primary conservative excision and radiation therapy for clinical Stages I and II breast cancer. Actuarial cancer-specific survival following salvage surgery was 72% at 5 years and 58% at 10 years. With a median followup of 7 years, further local-regional recurrences were observed in 20 of the 118 patients, many of whom could be treated by further surgery. Actuarial survival after recurrence was significantly influenced by initial clinical stage, as well as by the disease-free interval following primary therapy, but was similar for both premenopausal and postmenopausal patients and for patients treated by radical or breast-conserving salvage operations. For recurrences after the fifth year, actuarial survival following salvage surgery was 83% and 68% at 5 and 10 years, respectively. Survival for Stage I patients was favorable regardless of disease-free interval. It is concluded that recurrences in the breast following primary treatment with limited surgery and irradiation have a considerably more favorable prognosis than that of local failures after primary radical surgery. Suggestions for the management of these recurrences are presented.

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THE TREATMENT of early mammary carcinoma with preservation of the affected breast has become commonplace during the past ten years largely due to encouraging reports from several treatment centers having long experience with conservative techniques.[1-8] The recent publication of three randomized clinical trials, moreover, has established the validity of this treatment approach,[9-11] and has assured that breast-conserving therapy will become even more widespread.

Although curative therapy of local recurrences following primary radical mastectomy is seldom successful,[12-16] available evidence suggests that the prognosis of breast recurrence after tumorectomy and irradiation is considerably more favorable.[3,17-20] Since the treated breast remains at risk for an indefinite period of time, it is apparent that the optimal detection and therapy of breast recurrences represents an important facet of conservative treatment strategy. Thus, it is remarkable that the surgical management of local recurrences after breast-conserving therapy has received virtually no attention in the literature.

After 25 years of experience with more than 5000 conservatively treated patients with operable mammary carcinoma, we have had the opportunity to treat a large number of local recurrences.[18] The purpose of this article is to analyze the results of salvage therapy after initial management by local tumor excision and irradiation, to attempt to define prognostic factors, and to provide guidelines for the management of recurrence in the treated breast.

Materials and Methods

In order to provide adequate follow-up time after treatment of recurrence, this report has been restricted to patients whose primary therapy took place prior to the end of 1980. Excluded from analysis were all patients treated after that date, all patients referred by outside physicians exclusively for management of recurrence, patients whose primary tumors measured greater than 5 cm in diameter, as well as 1483 patients with moderately advanced lesions treated during the same time period by radiation therapy alone, without excision of the primary tumor.[2,21] Remaining as the basis for this

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report were 1245 patients with operable breast cancers in clinical Stages I and II (American Joint Committee, 1983)[22] treated between January 1963 and December 1980 at the Cancer Institute and associated clinics in Marseille, employing breast-conserving surgery followed by curative radiation therapy. Treatment techniques and long-term results of therapy have been described in previous publications.[2,21,23] Briefly, primary surgical treatment consisted of simple lumpectomy or wedge excision of the primary tumor, with or without limited axillary dissection. Radiation was performed using a telecesium or telecobalt unit, delivering 50–60 Gy (5000–6000 rad) to breast and regional nodes, followed by supplemental external beam irradiation to the tumor bed (20–30 Gy) and lower axilla (10–20 Gy).

Prior to January 1987, 143 of these 1245 patients (11.5%) developed recurrence in the treated breast. An additional 24 patients developed isolated recurrence in the ipsilateral axilla, and will not be considered further here. In 19 of the 143 patients (13.3%), a secondary operation was not performed, either because of the presence of distant metastases (11 patients), patient or physician preference (4 patients), or due to the local extent of the disease (4 patients). One hundred twenty-four patients were subjected to secondary operations for histologically proven breast recurrence, in the hopes of obtaining another chance at cure (salvage surgery). This report is restricted to 118 patients having had salvage surgery prior to December 1985.

Of the 118 patients having salvage surgery for proven recurrence, 56 were initially in clinical Stage I (T_1 N0) and 62 initially in clinical Stage II (T_1 N1 or T_2 N0-1). The average age of the patients at the time of primary treatment was 47 years. The mean interval between primary therapy and recurrence was 61 months. One hundred fourteen of the recurrences (96.6%) were described as being close to the site of the original primary tumor.

Salvage surgery consisted in 66 instances of a mutilating operation, either a simple mastectomy (8 patients), radical mastectomy (19 patients), or a modified radical mastectomy (39 patients). In 52 patients the salvage operation was conservative, consisting of wide excision in 34 patients and wide excision with axillary dissection in 18 patients. Conservative salvage surgery was introduced during the 1970s and has been increasingly employed for the treatment of isolated, small breast recurrences showing no signs of rapid growth. Although adjuvant hormone treatment was administered to selected patients, chemotherapy at time of breast recurrence was seldom employed.

Follow-up from time of salvage surgery ranged from 12 months to 20 years (median: 7 yr). Statistical analysis was performed using the life-table method of Kaplan and Meier.[24] Survival was calculated in terms of actuarial cancer-specific survival rates (hereafter referred to as actuarial survival), with patients dying of intercurrent causes while disease-free treated as censored observations at time of death. Patients dying of unknown cause were assumed to have died of cancer. The logrank test was employed to evaluate the differences between survival curves.[25]

Results

At the time of this analysis (January 1987), 34 of the 118 patients (29%) have developed proven distant metastases, and 38 patients have died, including 2 of intercurrent disease and 5 of unknown causes. The actuarial survival from time of salvage surgery was 72% at 5 years, and 58% at 10 and 15 years (Fig. 1).

With a median follow-up of 7 years after salvage surgery, 20 patients are known to have developed a second local or regional recurrence in the breast, chest wall, or axilla with or without the presence of distant metastases. This includes 8 of the 66 patients (12.1%) having had a secondary breast amputation and 12 of the 52 patients (23%) having been treated by breast-conserving salvage operations. Second recurrences after conservative salvage surgery could be treated by tertiary operations in ten instances.

Prognostic factors were investigated employing actuarial survival following the time of salvage surgery. The following parameters were analyzed (Table 1): age at time of primary therapy (less than 50 *vs.* 50 or greater, as a measure of menopausal status); initial clinical stage (I *vs.* II); histologic lymph node status at time of salvage surgery (positive *vs.* negative or undetermined); disease-free interval between primary therapy and recurrence (less than 3 years *vs.* 3–5 years *vs.* more than 5 years); and type of salvage operation (mastectomy *vs.* breast-conserving). Age and type of salvage operation had no significant correlation with the prognosis of breast recurrence. The slight advantage for patients treated by conservative salvage surgery may be explainable by the favorable selection of patients for these operations.

Disease-free interval and initial clinical stage represent the most significant prognostic factors for survival following breast recurrence. The outlook for recurrences occurring after the fifth year is significantly more favorable than that of recurrences operated prior to 3 years (Table 1). The prognosis of operable local recurrence in clinical Stage I patients was favorable even if the recurrence occurred prior to 5 years (5- and 10-year actuarial survival after salvage surgery: 70% and 65%, respectively, N = 28). For patients failing prior to 5 years, the unfavorable influence of axillary involvement at time of recurrence was statistically significant (5- and 10-year

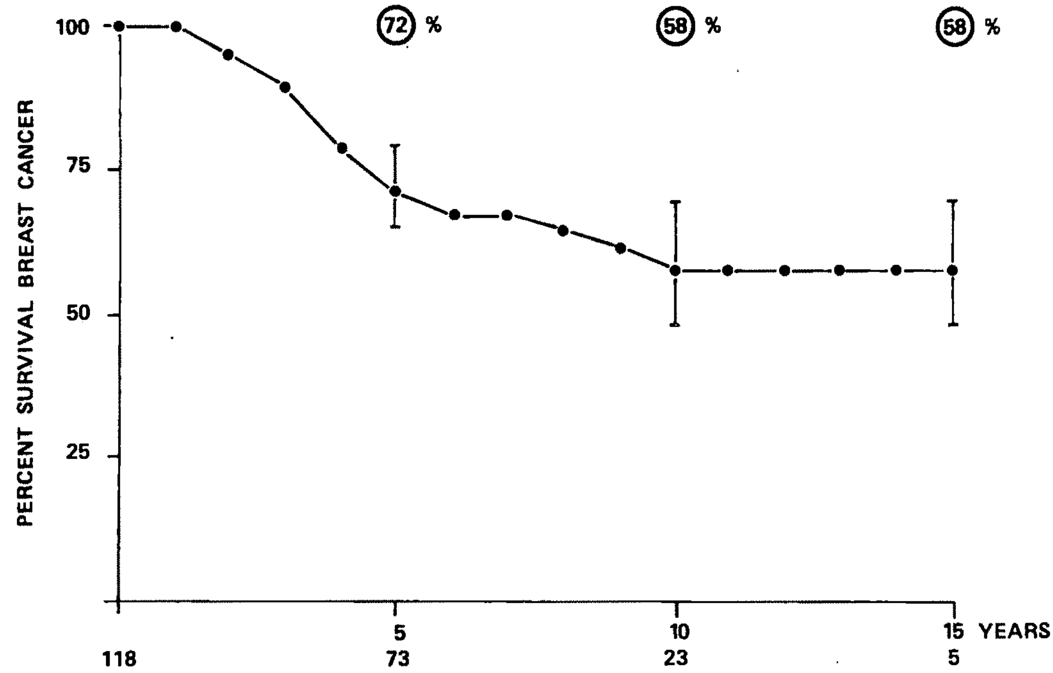

FIG. 1. Actuarial cancer-specific survival measured from the time of salvage surgery for mammary recurrence. The error bars represent the 95% confidence limits at 5, 10, and 15 years. The numbers at the bottom represent the number of patients alive at the beginning of the corresponding intervals.

actuarial survival after salvage surgery: 65% and 41%, respectively, N = 20) when compared to clinical Stage I patients with recurrences confined to the breast (5- and 10-year actuarial survival after salvage surgery: both 84%, N = 20, p value less than 0.01).

Discussion

Following treatment by primary radical surgery, the diagnosis of recurrence on the chest wall or in regional nodal areas connotes a grave prognosis for the breast cancer patient. Approximately one third of such patients have distant metastases diagnosed concomitantly with local recurrence, and the remaining patients who undergo *curative* treatment with surgery and radiotherapy have a poor outlook. Further therapy results in control of local disease in only about 50% of patients. Moreover, the majority of patients treated for apparently isolated local recurrence die of distant metastases, with overall survivals ranging from 21–38% at 5 years and 5–26% at 10 years.[12–16] Prevention of such recurrences through the use of adjuvant postoperative radiation therapy has failed to significantly improve survival rates,[26] suggesting that the appearance of local failure following primary radical surgery is the expression of a more aggressive tumor biology.

Such conclusions, however, do not necessarily apply to local recurrences following breast-conserving therapy. First, the percentage of inoperable recurrences is relatively small, with a range of 10–25% from the literature.[18] The high percentage of operable recurrences in our series (87%) probably reflects in part our program of follow-up examinations aimed at the early detection of such recurrences.[23] Second, local control following salvage surgery for recurrence after conservative therapy has been very satisfactory, with only 17% of our patients thus far having developed further local or regional disease manifestations. Although local control appears superior with secondary mastectomy, most patients having second recurrence following breast-conserving salvage surgery could be subjected to tertiary operations, and some have remained disease free. Follow-up is too

TABLE 1. *Actuarial Survival Following Operable Mammary Recurrence: Prognostic Factors*

Factor	N	5 Years (%)	10 Years (%)	
Age*				
<50	76	70	61	NS
≥50	42	77	48	
Clinical stage*				
I	56	78	70	$p < 0.01$
II	62	64	41	
Axillary recurrence				
No	87	73	55	NS
Yes	31	69	37	
Disease-free interval				
<36 Months	38	63	47†	
36–60 Months	30	72	61	
>60 Months	50	83	68†	
Salvage operation				
Conservative	52	79	64	NS
Mastectomy	66	68	54	

* Age and clinical stage at time of primary therapy.
† $p < 0.01$, 36 months *versus* 60 months.

short, however, to render judgment on the effectiveness of tertiary salvage surgery. If one includes the 19 patients not receiving salvage surgery, a total of 39 of the 1245 patients (3.1%) in this series had their breast disease uncontrolled by primary or secondary treatment. These results suggest that the combination of limited surgery and irradiation, with further surgery held in reserve in case of recurrence, provides control of local disease at least as good as that achieved by primary radical surgery.

A further contrast with postmastectomy recurrence is provided by the survival analysis of our patients, 72% of whom survived 5 years and 58% for 10 years following surgical treatment of recurrence. Actuarial breast cancer-specific survival appears to plateau after 10 years, suggesting that many patients may be cured by the salvage operation. It is likely, therefore, that local recurrence reflects a more virulent disease process only for a relatively small subset of patients, and that for many patients the disease course is not influenced by the appearance of failure in the breast. In particular, conservatively treated Stage I patients continue to have a favorable prognosis despite local recurrence.

Our analysis of prognostic indicators demonstrates that the disease-free interval between primary treatment and recurrence is a very significant determinant of survival following salvage therapy. The importance of disease-free interval has previously been well documented in analyses of recurrences following radical surgical therapy.[13–15] Since the treated breast remains at risk for recurrence for an indefinite period, it is possible that late local recurrence will be observed more commonly following breast-conserving therapy than after primary radical surgery. Thus, it is important to realize that local failure after the fifth year has a very favorable prognosis, with actuarial survival of 68% 10 years following treatment of recurrence. We have found that such late recurrences have a significantly better prognosis than that of contralateral breast cancer in this series of patients (Spitalier J-M, Kurtz JM: unpublished observation, January 1987). The continued risk of ipsilateral breast recurrence beyond 5 years, therefore, does not represent a cogent argument against breast preservation. We do not expect that late recurrences will in any way prejudice the current early results favoring this form of treatment.[9–11] The distinction between late recurrence and *new* tumor formation in the ipsilateral breast is extremely difficult, and may be mainly of academic interest. This will be the subject of a subsequent report.

Prognosis of breast recurrence during the first 5 years appears to depend to a large extent upon the status of the axilla. The outlook is unfavorable for patients initially in clinical Stage II, as well as for patients having histologically involved axillary nodes at time of salvage surgery. Thus, patients having been initially at high risk for axillary metastases, or those having suffered proven recurrence in the axilla, have a poorer prognosis than early-stage patients, or those developing recurrence confined to the breast. These results confirm our previous observations,[18] as well as those of Clark et al., who showed that isolated breast recurrence had no significant impact on the course of the disease in the Toronto series.[17] Since the majority of our patients did not have axillary dissection at the time of initial therapy, a more precise evaluation of the prognostic significance of nodal status is not possible.

There are no published guidelines for the management of recurrence following breast-conserving therapy, perhaps reflecting a supposition that failure in the breast dictates mastectomy. We have found that wide excision of selected localized breast recurrences, however, can be associated with satisfactory results.[27] Patients desiring a second chance at breast preservation may be offered this treatment option, provided that the recurrence is 2 cm or smaller in diameter, mobile, and without signs of rapid growth or extensive axillary adenopathy. Many of the 20–30% of patients developing second breast recurrence after conservative salvage surgery can be offered a potentially curative tertiary operation. Less favorable recurrences should be treated by total mastectomy. Independent of the treatment of the breast, the axilla should be dissected at the time of mammary recurrence, provided that it had been previously undissected or if clinically suspicious findings are present. Isolated axillary failure should be treated by axillary dissection if there is no clinical or radiographic evidence for recurrence in the breast.

The role of adjuvant medical therapy at time of local failure has never been formally investigated, and such treatment has not been employed in any consistent fashion in our institution. Additional therapy following surgery for late recurrence is generally unnecessary. For the less favorable recurrences occurring during the first 5 years, especially those with axillary failure or prior evidence of lymph node involvement, adjuvant systemic treatment is generally recommended, although evidence for its efficacy in this setting is lacking. The hormone receptor status and age of the patient dictates whether oophorectomy, hormone therapy, or combination chemotherapy is employed as adjuvant treatment.

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Book Reviews

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Cope's Early Diagnosis of the Acute Abdomen, 17th ed. William Silen. 290 pp. New York: Oxford University Press. 1987. $14.95.

I HAVE a large library of surgical texts and refer to them often. I have and value the charming *The Acute Abdomen in Rhyme* by the pseudonymous *Zeta* who is well known to have been Sir Zachary Cope. Cope's classic *Early Diagnosis of the Acute Abdomen* is now in its 17th edition, and but for the good fortune of having been asked to review it, I should still be ignorant of this gem now in its second edition in the capable hands of William Silen. I had known of the book—of course, who has not—but considered from first hearing of it that a book with that title did not have much to teach me. How wrong I was!

The book is a model of simplicity, lucidity, and soundness, and the language is a joy. Perhaps senior surgeons will consider that Cope and Silen are preaching to the converted. For them I will say that it may well be that a reading of this little book will show them an example of how really to teach. As for students and house officers, let them learn how really to make a diagnosis and how much can be learned from history and sophisticated physical diagnosis before, and often without, resorting to the modern panoply of diagnostic equipment, as well as the when, why, and which of such resort.

A few quotations will transmit the marvelous flavor. "The pulse is too optimistic a friend to be relied upon for guidance either in diagnosis or prognosis in the early stages of abdominal disease . . . many if not most, patients with acute lesions of the abdomen have a normal pulse during the early stage. . . ."

"In many medical centers, there are standard algorithms for laboratory and radiologic investigations . . . patients with abdominal pain receive many unnecessary, expensive and sometimes misleading laboratory tests. . . . It is imperative that the clinician understand that *laboratory tests will never substitute for clinical evaluations of the patients* . . . x-ray studies are *not* necessary or desirable in all patients with abdominal pain." Lives would be saved if every medical student in the United States read and remembered the statement that in *colic* whether intestinal, urinary or biliary, "though occasionally rigid during the paroxysms the abdominal wall is soft between bouts of pain."

Easy to read and full of good sense, the book is a distillation of the massive clinical experience of two master surgeons. Abundant line drawings and reproductions of roentgenograms and sonograms illustrate the text, which is unencumbered by graphs, tables, formulas, statistics, or references. The experienced surgeon will enjoy comparing his own opinions, procedures, and priorities with those of Cope and Silen. The less experienced are not likely to find anywhere so much useful wisdom in so few pages.

Mark M. Ravitch, M.D.
Pittsburgh, Pennsylvania

Surgical Application of Lasers, 2nd ed. John A. Dixon. 376 pp. Chicago: Year Book Medical Publishers. 1987. $49.95.

THIS MONOGRAPH is edited by Dr. John A. Dixon who is clearly the leader in the use of lasers in medicine and surgery. He has been a major force in the education of physicians and surgeons concerning the use of lasers in clinical practice, and the second edition of this monograph continues that tradition. As with the first volume, it provides the background for clinical use of lasers in surgery. In addition, it contains an excellent update of developments in this advancing field during the past 5 years. Twenty other clinical laser specialists have contributed to this text, which again reviews the basic science of laser technology and then discusses its use in various surgical disciplines.

The chapters on historical background and instrumentation are well done, and the basic science section is complete and quite readable. In the section on safety, Dr. Dixon emphasizes the dangers of lasers and the need for consistent observation of appropriate precautions when using lasers. The points regarding establishing a laser system in the institution are important and helpful.

Dr. Dixon and the other contributors have had a wide and successful clinical experience. The clinical sections are commendably complete, and the most recent advances are cited as well as problems that need to be addressed in each specialty. The chapter on photodynamic therapy is excellent and is an important component.

The illustrations are quite good, and the color plates that are included in one section might well have preferentially been placed with the specific chapters to which they apply. In summary, this monograph brings the reader up-to-date on the developments in laser therapy during the past 5 years, and the editor has achieved this goal admirably.

Walter G. Wolfe, M.D.
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Essentials of Plastic, Maxillofacial, and Reconstructive Surgery. Nicholas G. Georgiade, Gregory S. Georgiade, Ronald Riefkohl, and William J. Barwick. 1189 pp. Baltimore: Williams & Wilkins. 1987. $117.95.

THIS IS AN ambitious attempt to cover in one volume the entire field of plastic surgery. The four authors, all from Duke University, have collected input from 133 contributors and molded it into an informative, readable, and comfortable volume. Fortunately, the inevitable unevenness in the quality of the chapters has been minimized, probably due to "the strong hand of the principal editor, Dr. Nicholas G. Georgiade," to quote from the foreword by David C. Sabiston, Jr., M.D.

The book is divided into nine sections: Basic Principles, Skin and Soft Tissues, Head and Neck, Aesthetic Surgery, Breast Surgery, Surgery of Genitalia, Microsurgery, Trunk and Lower Extremity, and Practical Concepts of Plastic Surgery Practice.

The 94 chapters are written with as much detail as could be expected in such a comprehensive volume. The drawings, tables, and sketches have been selected effectively to amplify the text without cluttering it. None of the chapters is monographic in scope, but the bibliographies are selective and mostly current.

The two sections on Head and Neck (388 pages) and Microsurgery (234 pages) occupy over half the book and reflect the major interests and contributions of the Duke unit. The section on Breast, another area of their special interest, is well presented. The embryologic descriptions in several of the sections are noteworthy.

This text will be useful for all residents and practitioners in plastic, maxillofacial, and oral surgery. They will find it a convenient final source for some subjects, and a valuable starting point for the others. The price of $117.95 seems reasonable.

JOSEPH E. MURRAY, M.D.
Boston, Massachusetts

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The numbers paint a sobering picture. Deep Vein Thrombosis (DVT), often the precursor of pulmonary embolism, occurs 2.5 million times a year in the U.S. Between 300,000 and 600,000 hospitalizations are a direct result. Approximately 150,000 deaths annually are traced to pulmonary embolism.

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The validity of risk assessment arises from the silent nature of DVT. In fact, up to two thirds (⅔) of the real incidence of DVT often go undetected. Stasis, coagulation changes and blood vessel damage are the principal causes. Consequently, factors such as age, immobility, obesity and other medical conditions that can contribute to causal ingredients can be clearly identified.

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In effect, the evidence supports establishing clinical guidelines including physical approaches to prophylaxis. At higher levels of risk and where side effects are not at issue, pharmaceuticals can provide an added measure of effect.

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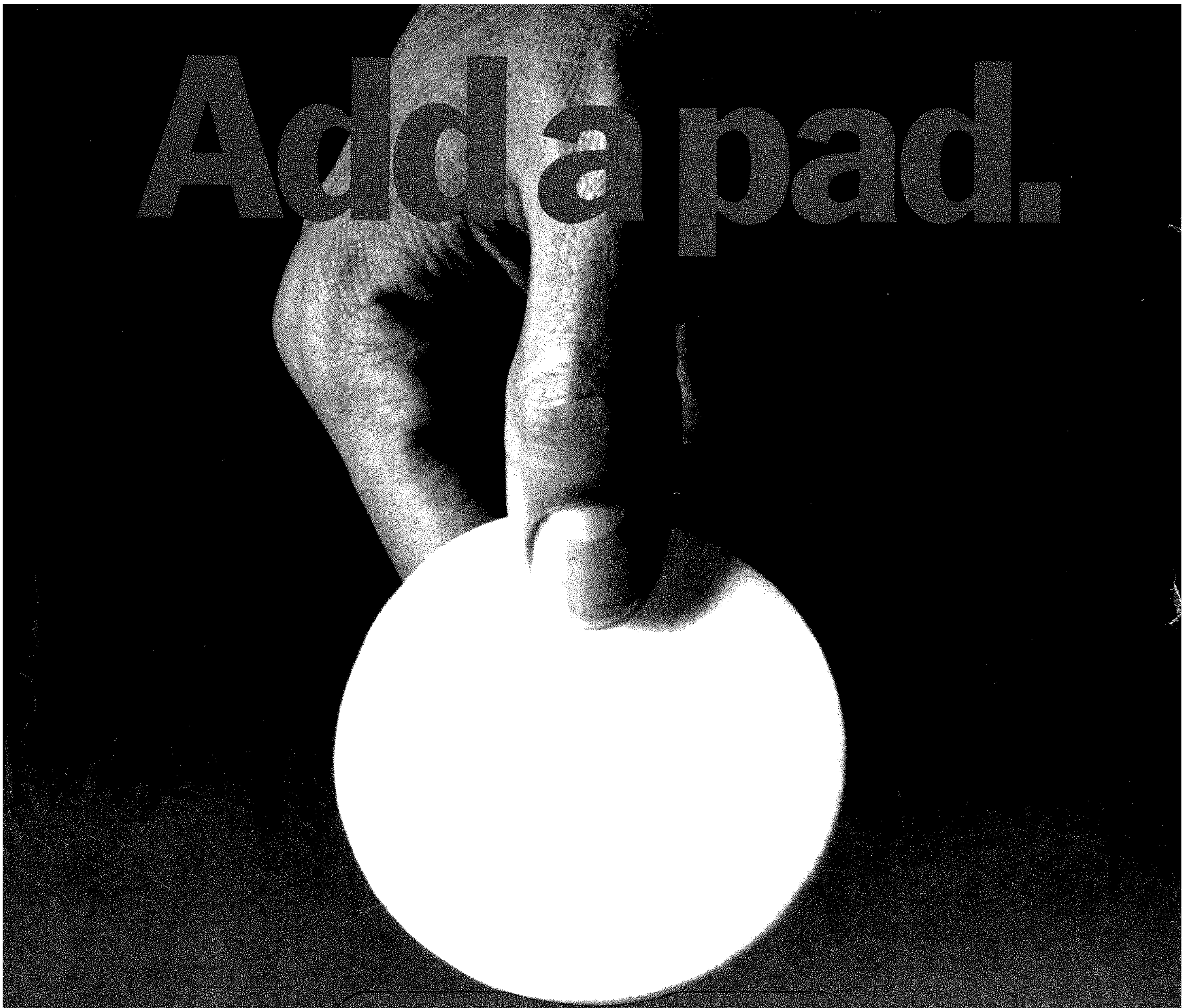

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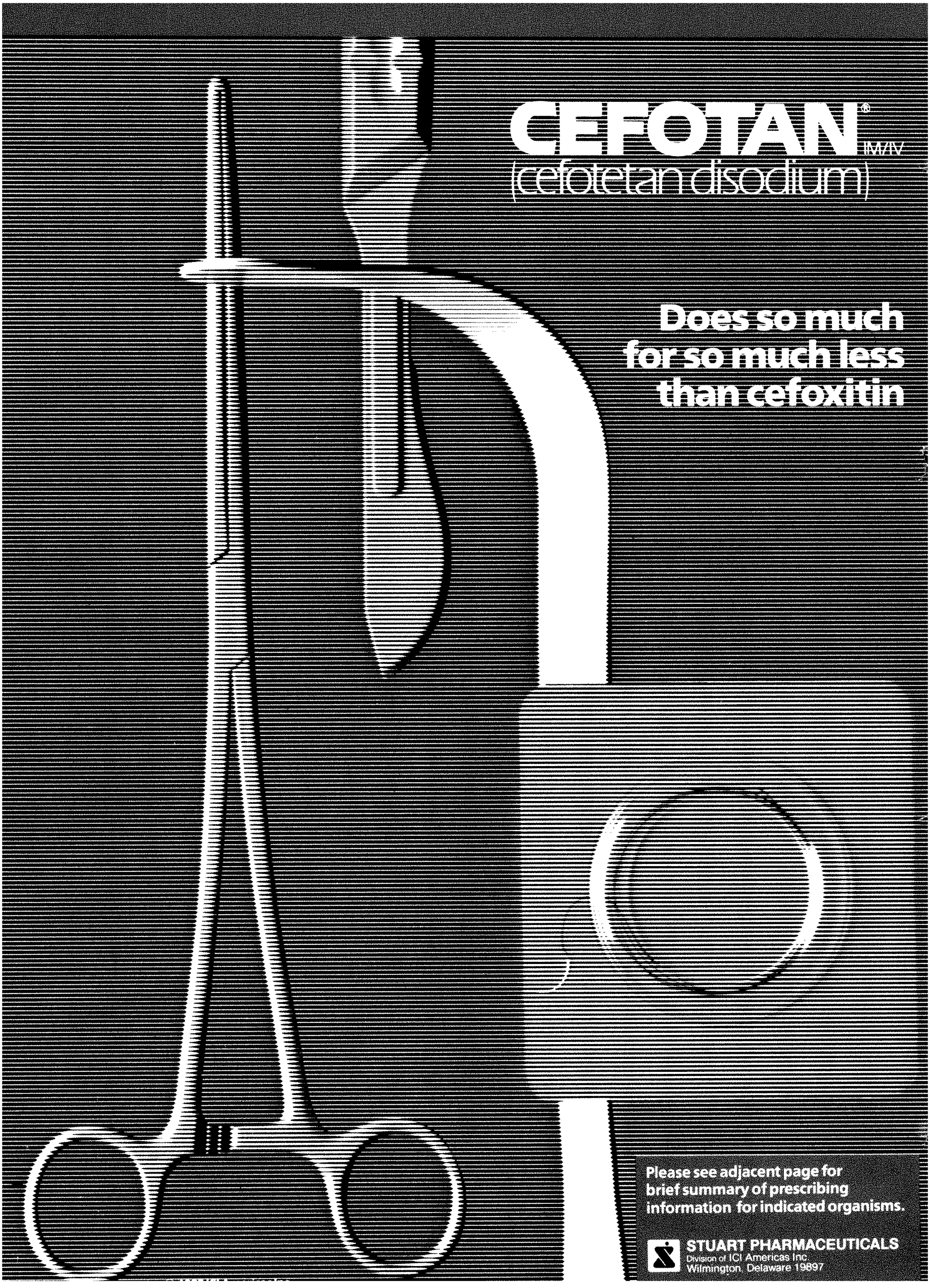

Please see adjacent page for
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information for indicated organisms.

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BRIEF SUMMARY

INDICATIONS AND USAGE

TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary tract infections caused by *E coli, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris, Providencia rettgeri*, and *Morganella morganii*).

Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.

Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis,** *Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.

Gynecologic infections caused by *Staphylococcus aureus*† (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis,** *Streptococcus* species (excluding enterococci), *E coli, Proteus mirabilis, Neisseria gonorrhoeae, Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*), *Fusobacterium* species,† and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species†).

Intra-abdominal infections caused by *E coli, Klebsiella* species (including *K pneumoniae*†), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*).

Bone and joint infections caused by *Staphylococcus aureus.*†

***NOTE:** Some strains of *Staphylococcus epidermidis* are resistant to cefotetan.

† Efficacy for this organism in this organ system was studied in fewer than ten infections.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.

PRECAUTIONS

GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state. Prothrombin times should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels of Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approx 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approx 2-4 times the usual human dose), only 1 of 10 treated animals was affected, and the degree of degeneration was mild. Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In clinical studies the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5 percent of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4 percent of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2 percent of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2 percent of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than one percent of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

DOSAGE AND ADMINISTRATION

TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dose*	Every 12 hours
10-30	Usual Recommended Dose*	Every 24 hours
<10	Usual Recommended Dose*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED

CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21)

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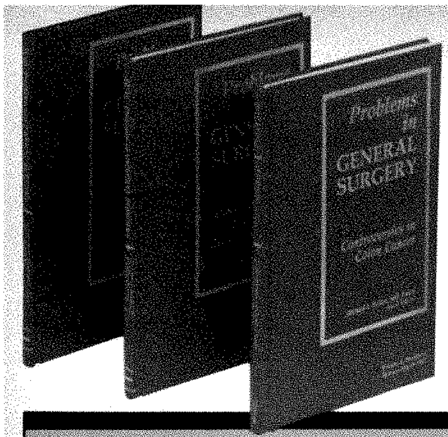

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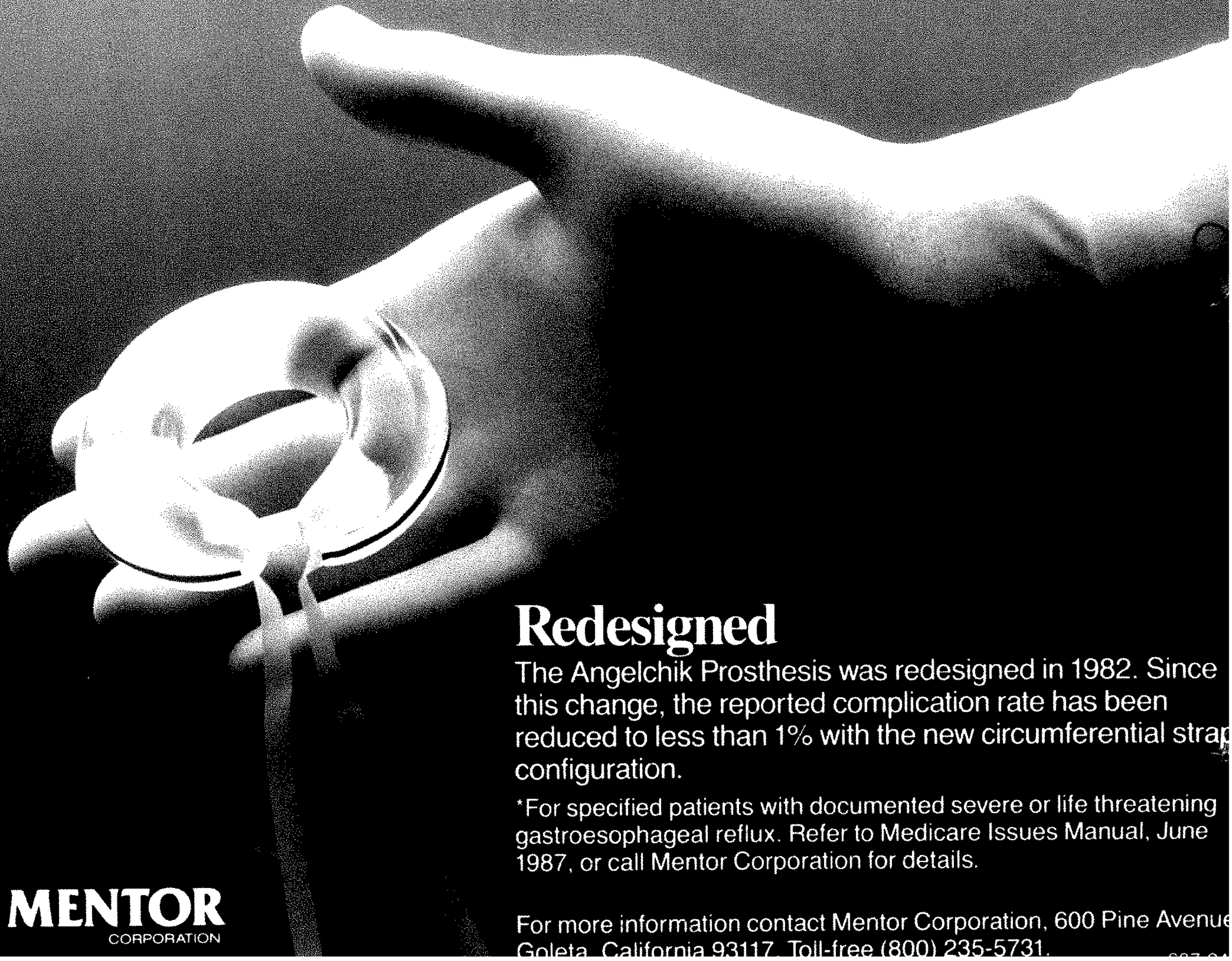

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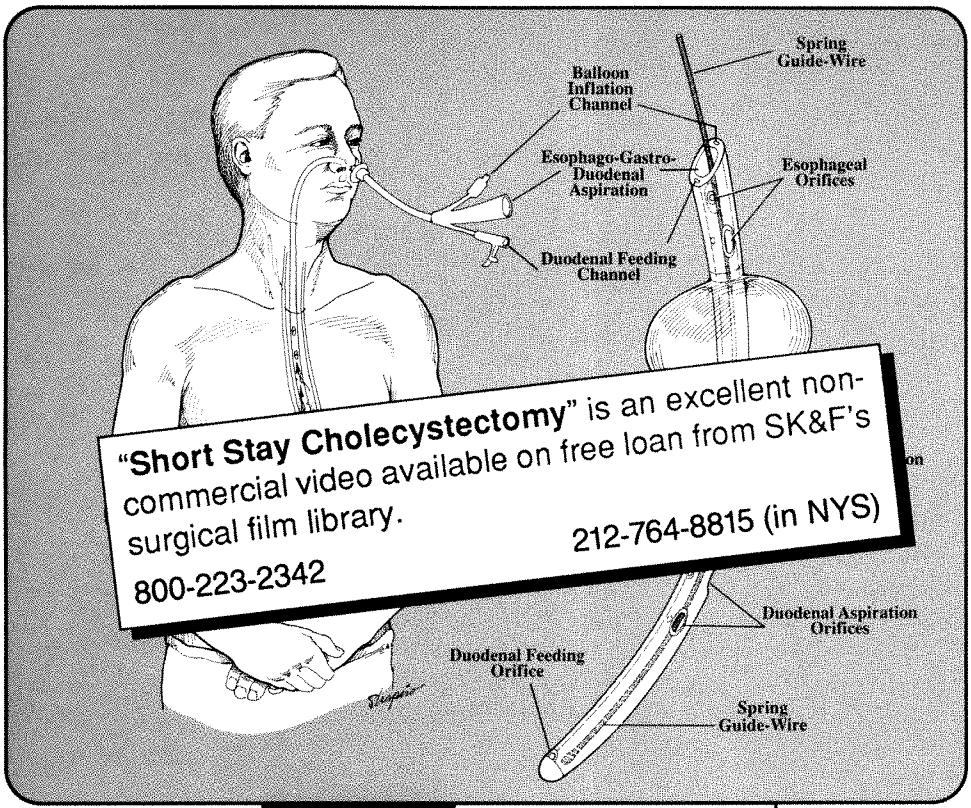

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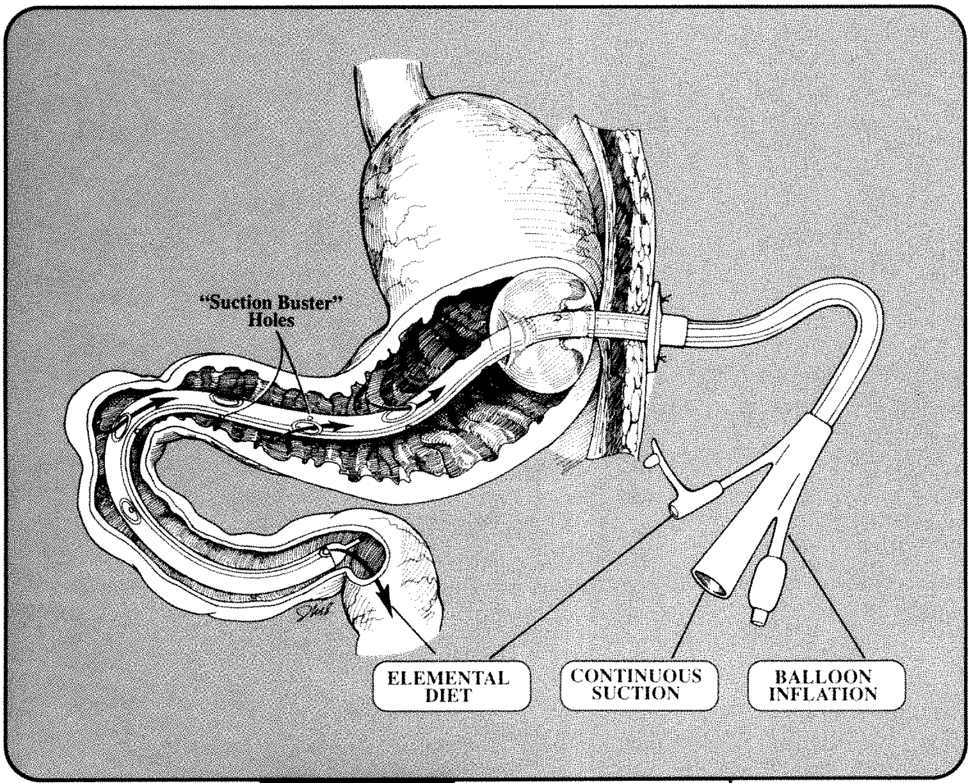

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CASE # 24 **AGE:** 55 **SEX:** FEMALE

DIAGNOSIS: CECAL CARCINOMA

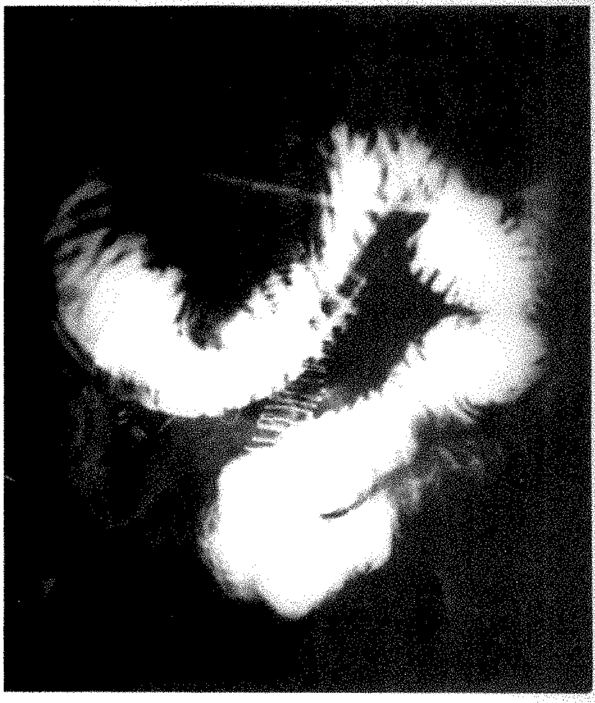
SYMPTOMS: ANEMIA (Hg 6 gm/dl)

OPERATION: RIGHT HEMICOLECTOMY & GASTROSTOMY

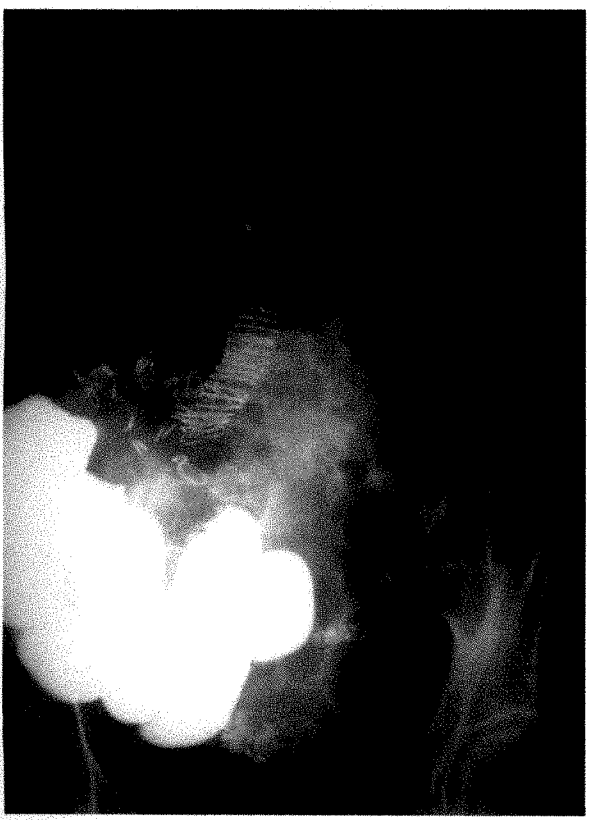
The patient had a right hemicolectomy with stapled (U.S. Surgical Corp) anastomosis and fascia closure and a MOSS® gastrostomy tube. The stomach and proximal duodenum were aspirated, with immediate simultaneous feeding into the distal duodenum.

Barium feeding 5 hours postop documented adequate motility. The deliberate excess was totally removed. No contrast (i.e.: excess feeding) escaped efficient aspiration within the proximal duodenum, to reflux into the stomach. (Figure A) Serial motility study showed barium had traversed the anastomosis and colon, and already was exiting in a spontaneous bowel movement by 21 hours postop. (Figure C)

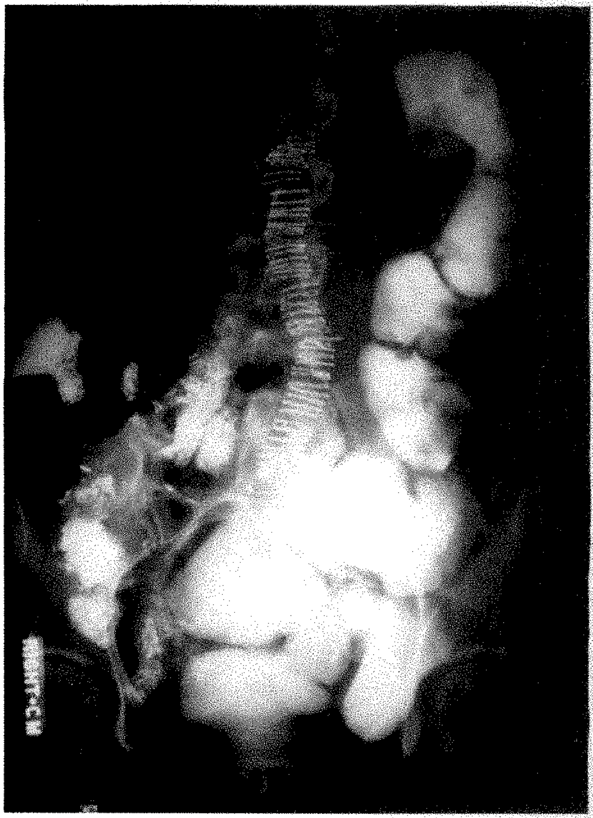
She received 300 ml/hr of Vivonex TEN (Norwich Eaton Pharm), absorbed 5,000 kcal the initial 20 hours, and then tolerated a general diet. She was the 4th patient discharged uneventfully 24 hours after bowel resection and reanastomosis.



A. Study @ 5 minutes (5 hours postop).
Note efficient removal of all excess barium, with none reaching the stomach.



B. Motility @ 4 hours (9 hours postop).
All barium is within the ileum.



C. Motility @ 16 hours (21 hours postop).
Barium is exiting in a spontaneous bowel movement.

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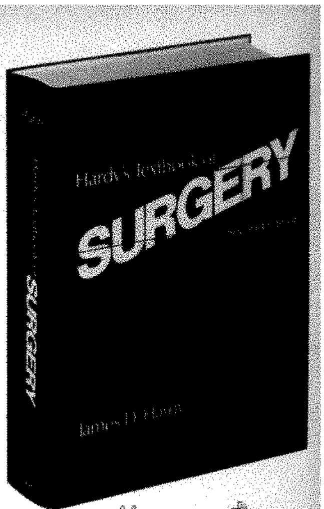

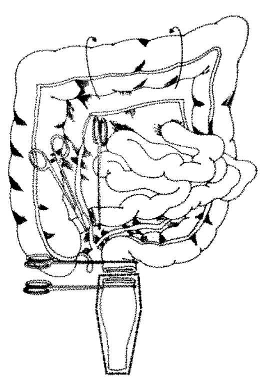

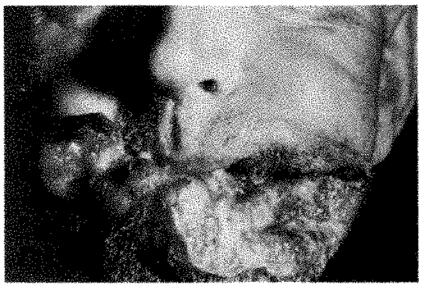

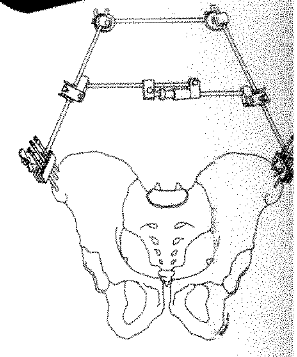

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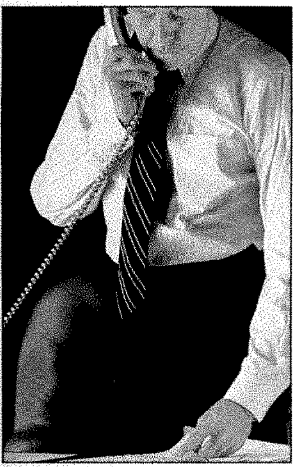

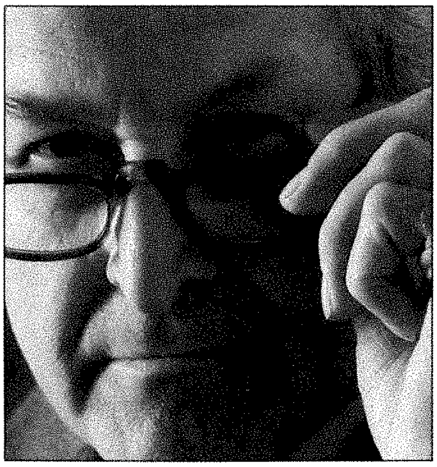

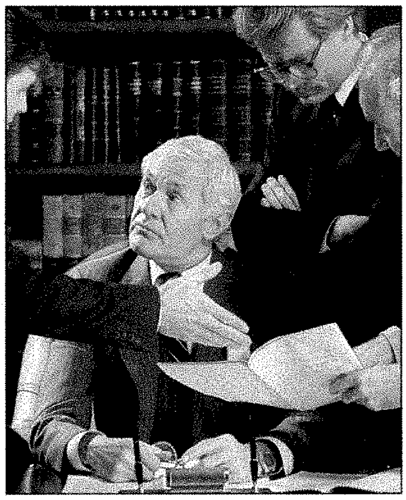

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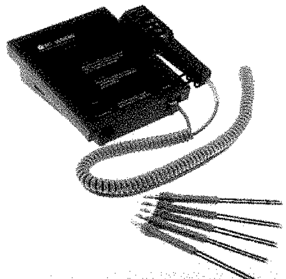

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[1] National Center for Health Statistics for 1985.

[2] A complete list of clinical evaluators is available upon request.

April 1988
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Annals of Surgery

What's New
In General Surgery

Current Laser Applications in General Surgery

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From the University of Utah Department of Surgery Laser Institute, and the Laser Section, Salt Lake Veterans Administration Medical Center, Salt Lake City, Utah

THE POSSIBILITY of application of lasers as a surgical instrument has intrigued surgeons since the introduction of the first CO_2 medical lasers in 1967.[1] Laser surgery has been characterized by a great amount of basic research and clinical application in nearly every surgical specialty. Like most new instruments, procedures, or medications, laser surgery has gone through the usual cycle of abundant optimism and expansive claims, followed by complications and criticisms, followed by a gradual transition into realistic expectations and utilization. Fortunately, much of media hype and sensationalism regarding lasers in medicine has subsided and been replaced by careful evaluation and comparison with the established modalities and techniques. In some situations, such as endoscopic laser control of gastrointestinal (GI) bleeding, a reasonable number of prospective controlled randomized trials have been carried out. In many other instances, such as endoscopic laser pancreatic cystogastrostomy, however, the number of cases in which lasers have been employed are few and results almost anecdotal. Maturity in each specialty of each procedure must be evaluated.

A discussion of laser applications in general surgery must first approach the difficult task of defining general surgery. For the purpose of this paper, the American Board of Surgery description, which includes "general processes involving wound healing, hemostasis, neoplasia, and surgery of endocrine system, hernia, vascular system, gastrointestinal tract, abdominal organs and endoscopic principles and applications," will be utilized.[2] Lasers are employed relatively infrequently for limited indications by the traditional surgeon using incisional techniques. When one considers, however, the disease processes being treated by endoscopic laser techniques that would have formerly been managed by the general surgeon, a great impact on this specialty is evident.

Laser Fundamentals and Instrumentation

The principles necessary for the formation of the concept of lasers were noted as early as the 19th century with the presentation of Bohr's theory of optical resonators. In 1917 Einstein proposed the concept of stimulated emission of light.[3]

An extensive discussion of subsequent developments in laser physics is not consistent with this clinical review. In general, however, an atom, molecule, or ion in its resting energy state or ground state is excited to a higher energy state by the absorption of thermal, electric, or optical energy. After energy is absorbed, an atom, mole-

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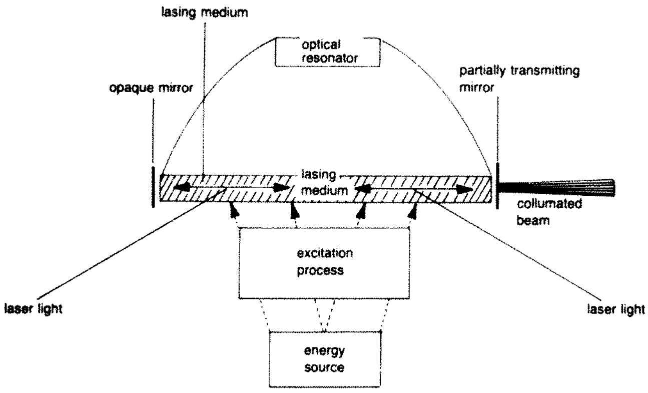


FIG. 1. Outline of laser operation. Energy source produces excitation process with excitation of lasing medium. Photons from lasing medium reflect off mirrors and are released through partially transmitting mirror (*right*).

cule, or ion spontaneously returns to a ground state and thereby liberates absorbed energy as a photon. The energy so created emerges as light that is coherent, of one wavelength, and in temporal and spatial phase (Fig. 1). This allows the beam to be focused, made divergent, or collimated (directed in parallel fashion, not focused or divergent). Such coherent light then may be focused on mirrors or flexible quartz rods (fiber) transmission.

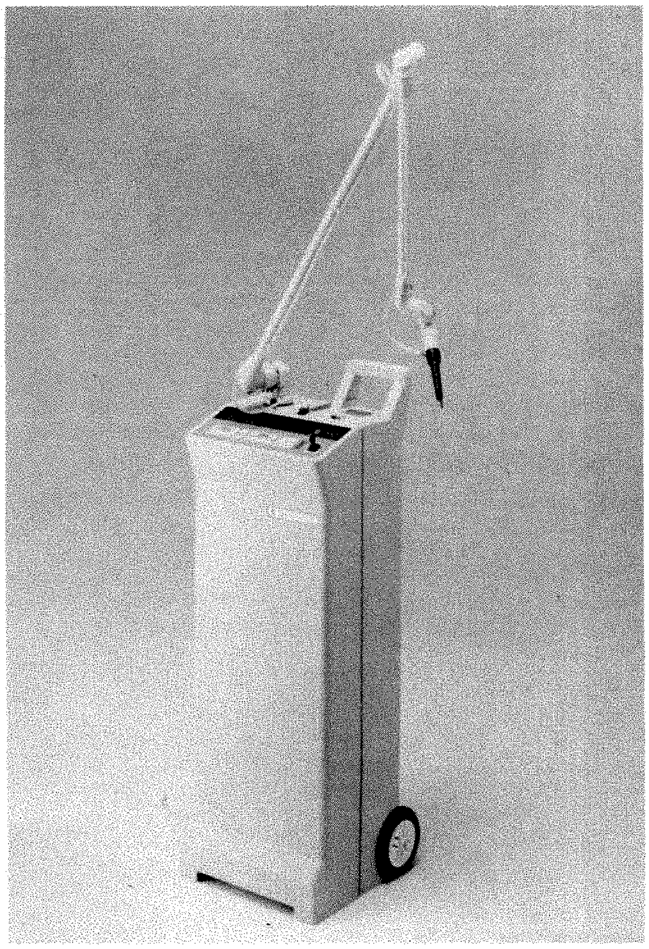


FIG. 2. Compact, portable 30 watt CO_2 laser with articulating arm for general surgical use (Sharplan Model 1020).

As laser light impinges upon tissue it may be reflected, absorbed, scattered, or transmitted.[4] The amount of absorption is determined by substances called chromophores. Two of the most common chromophores in tissue are hemoglobin and water.

Lasers in common use are the CO_2, argon, and neodymium YAG (Nd:YAG) lasers. Carbon dioxide laser energy (10.6 μm) is ideal for cutting and vaporization because it is heavily absorbed by water.[5] Unfortunately, CO_2 energy transmission requires a series of mirrors and an articulating arm for transmission. Although digital control of handpieces and articulating arms is fairly good, this method is still awkward in abdominal and other applications. Because of absorption by water, thermal injury from a given amount of energy from this laser is relatively superficial, ranging from 50 to 100 μm in depth. Small portable laser devices are available (Fig. 2).

Argon laser light (458–515 nm) is very heavily absorbed by hemoglobin and is especially useful in nonbleeding vascular lesions when precision and minimal depth of penetration (about 1 mm) are required.[6] Although heavily absorbed by blood, argon laser energy can be transmitted readily through water, gastric fluid, urine, *etc.*

The Nd:YAG laser (1.06 μm) has less specific absorption by water and hemoglobin than the preceding two lasers.[7] This results in a depth of thermal injury of approximately 3 mm in most tissues, which is useful for coagulation of large volumes of tissue such as in palliative coagulation of esophageal and colonic carcinomas.

While most laser applications are made using a noncontact technique, there has been recent introduction of a variety of sapphire or ceramic contact tips for handheld or endoscopic use, which allow for application of pressure to bleeding vessels or highly focused laser energy on the tip of a laser scalpel to minimize diffusion and laser tissue injury (Fig. 3).[8]

Unlike many surgical devices, the laser may harm surgeons and operating personnel as well as patients.[9] Goggles or appropriate eye wear with filters capable of protecting against the wavelength in use must be worn at all times. Access to the operating suite must be controlled so that individuals without appropriate eye wear do not enter. Surgical instruments in the field must be of a nonreflective type. Operating room drapes must be moistened or inflammable. Endotracheal tubes must be either metal or wrapped with reflective tape to prevent ignition or melting.[10]

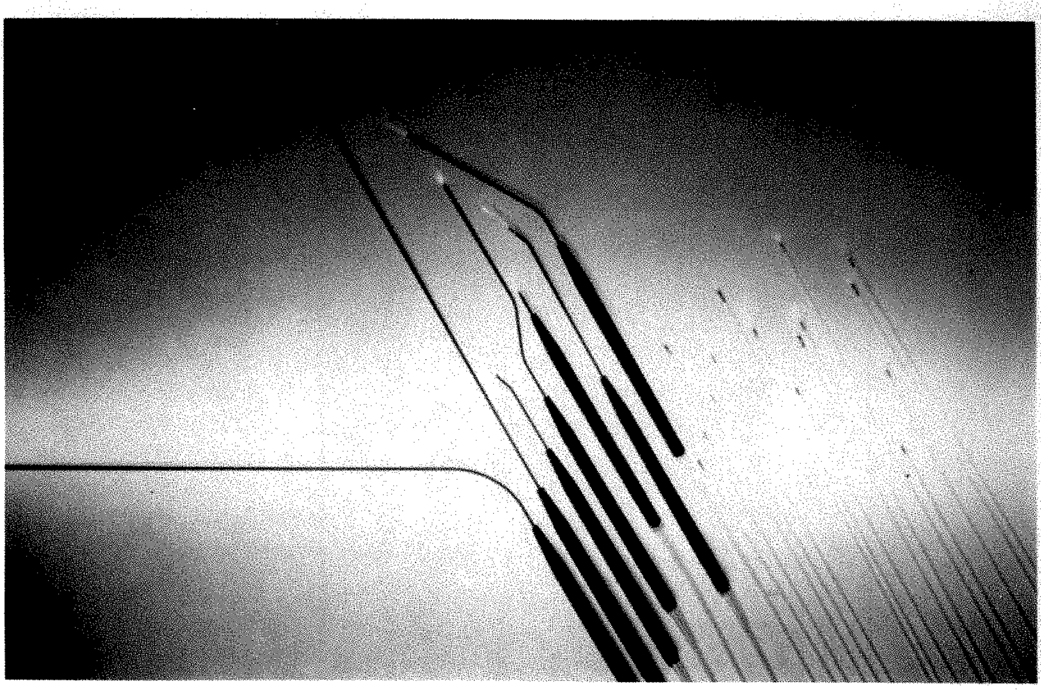


FIG. 3. Variety of handheld (left and endoscopic right) sapphire tips for operative and endoscopic use (Surgical Laser Technologies).

Where lasers are to be widely utilized, it is necessary to have a central organization to provide for laser safety, scheduling, maintenance of laser devices, fiber preparation, credentialing of users, and in-service training of personnel. The complexity of this organization depends upon the number of lasers and frequency of usage. Such units are usually managed by a part-time director and laser safety officer, with an advisory committee made up of representatives of the specialties using the laser. Shared use of lasers can greatly reduce cost per patient.[11]

Basic Surgical Processes

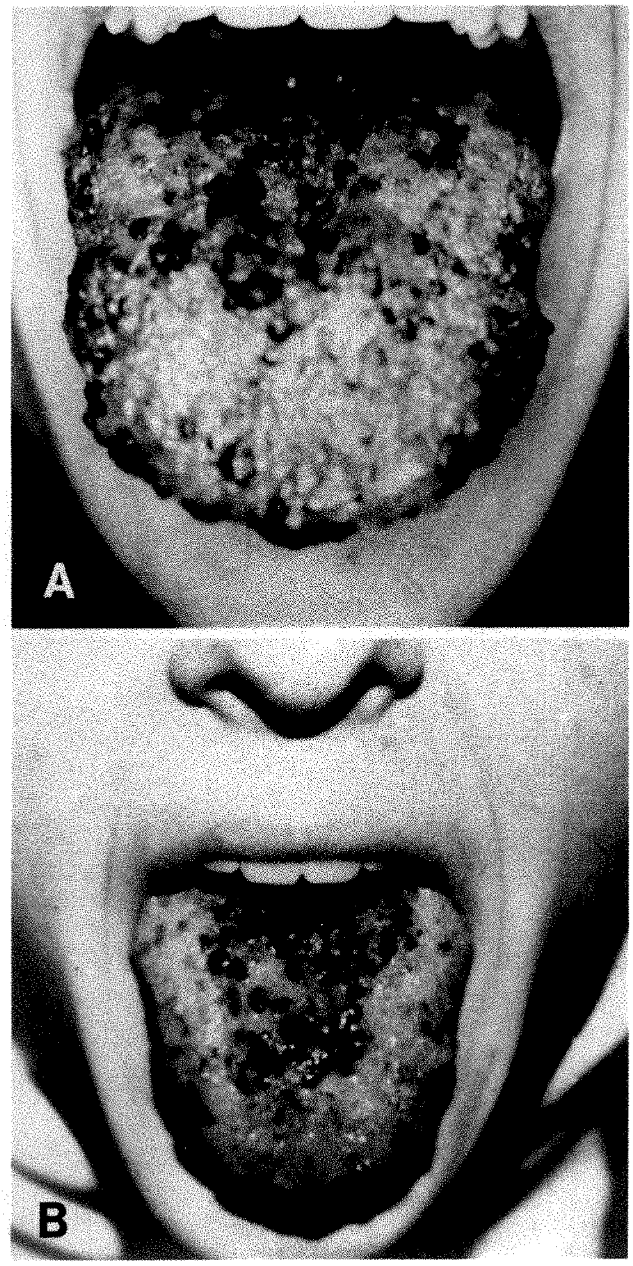
As compared with the scalpel, laser cutaneous incisions demonstrate delayed epithelial migration, prolonged period of wound phagocytosis, and decreased tensile strength up to 7–28 days.[12] This is probably due to thermal damage from the laser. After that period wound healing as measured by tensile strength is similar with both laser and scalpel.[13] The clinical significance of these findings is obscure at this time. The most practical recommendation is that cutaneous sutures remain in for an additional 3–5 days in laser incisions to allow for the more prolonged healing processes described.

Several authors suggested that low energy "soft or cold" lasers may result in biostimulation with acceleration of the rate of healing of wounds.[14,15] Mester and Mester reported that phagocytosis by leukocytes increases in response to helium-neon or argon laser at 0.5 J/cm^2 and that an accelerated growth of fur on mice occurs in response to exposure to low energy radiation.[16] Kana irradiated skin wounds in rats with the helium-neon laser at 45 mw/cm^2 and reported a statistically significant stimulating effect on collagen synthesis in the wound as measured by rate of wound healing and hydroxyproline content.[17]

The very considerable experience of the Mester's in patients with cold laser stimulation of healing in indolent leg and decubitus ulcers is interesting and merits continued observation. The application of argon laser at 4 J/cm^2 twice a week in over 1300 patients resulted in healing in a variety of lesions that were resistant to conventional treatment.[18] However, the problem of documentation in this area is great and statistical analysis difficult. So little is known of this type of laser/tissue interaction that one should be careful concerning premature acceptance or dismissal of biostimulatory effects. As is the case with many therapeutic agents, dosage may be critical with one energy dose being stimulatory and a slightly different one of the same wavelength being inhibitory or destructive.

Laser energy, especially at wavelengths in the hemoglobin absorption peaks, ruptures red blood cells, damages platelets, and activates clotting cascades with thrombus formation.[19] Endothelial damage, protein denaturation, shrinkage, and perivascular edema likewise contribute to vessel closure. Each laser, however, has limitations as to the size of vessels that can be controlled. The defocused CO_2 laser can coagulate vessels up to approximately 0.5 mm; the argon laser up to 1 mm; and the Nd:YAG laser up to 3 mm.[20]

Despite numerous anecdotal clinical references to decreased blood loss with laser surgery, statistical evidence is not readily at hand. One controlled study on burn excision in pigs showed a significant reduction in blood



FIGS. 4A and B. *A*. Lymphangioma of tongue with recurrent bleeding. *B*. Three months following Nd:YAG laser therapy. Marginal 3 cm of tongue treated by spot technique. Central portion of tongue untreated.

loss when experimental burns were excised with the argon laser as compared with electrosurgery.[21] There are several reports of reduced blood loss in experimental and clinical hepatic resections utilizing the CO_2 or Nd:YAG laser.[22,23] On the other hand, a controlled study using the Nd:YAG laser in canine experiments failed to show a statistically significant reduction on blood loss when the laser was employed for hepatic surgery in a noncontact fashion.[24] Decreased blood loss was recorded in experimental partial splenectomy[25] and clinically in mastectomy.[26]

One important area of laser hemostasis involves emergency surgery in patients with hemophilia, thrombocytopenia, or other coagulopathies. Due to vessel closure by thermal factors, it is reported that bleeding can be controlled by lasers during urgent procedures in such individuals. Kiefhaber stated that a platelet count of 25,000 is the minimum necessary for laser hemostasis in the GI tract.[105] A recent study involving the use of the CO_2 laser in surgery in hemophiliac patients undergoing synovectomy of the knee noted a significant reduction in blood loss, necessity for blood factors, time of operation, and duration of hospitalization compared with conventional techniques.[27]

Early reports suggested that infection in laser wounds would be reduced due to high temperatures created with bacterial "sterilization."[28] Shultz et al. studied the effect of Nd:YAG laser energy on three bacterial strains: *Staphylococcus aureus, Escherichia coli,* and *Pseudomonas aeruginosa.*[29] Energy fluence of 1667–3333 J/cm^2 resulted in a 2–8 log decline in a number of viable bacterial colonies. *P. aeruginosa* was the most sensitive to the Nd:YAG laser.[29] A study employing the CO_2 laser with *E. coli* and *S. aureus* also showed a dramatic reduction of bacteria.[30] It appears that lasers may reduce bacterial colonization at the time of incision, but experimental laser wounds subsequently contaminated have a higher incidence of infection.[31] Sterilization by laser is unlikely, but reduction of bacteria in necrotic infected wounds is probable.

It is evident from experimental and clinical studies that tumors can be coagulated or vaporized using the thermal effects of the laser.[32] Controlled studies in the bladder[33] and gastric cancer are in progress to determine comparative efficacy of endoscopic laser and conventional treatment. Sealing of lymphatics by lasers in tumor surgery is still uncertain. Frishman et al. reported a reduction in pulmonary metastasis when the CO_2 laser was used to excise experimental subcutaneous fibrosarcomas.[34] Oosterhuis et al., in a careful study of Cloudman melanoma cell dispersion, reported that CO_2 laser was "no worse than the conventional scalpel" in dissemination of cells from the incised tumor.[35] In a recent experimental study comparing the effect of circumferential Nd:YAG laser and electrocautery applications around the dome of the urinary bladder in restricting lymphatic migration of carbon particles, there was a statistically significant lesser degree of particulate migration through the laser barrier as compared with electrocautery.[36] Lanzafame et al. found that wound recurrence of experimental tumors in Fisher rats was significantly reduced by CO_2 laser excision.[37] Viable tumor cells were not found in the smoke plume during tumor vaporization with the CO_2 or Nd:YAG laser.[38,39]

Possible carcinogenic effects of lasers must be consid-

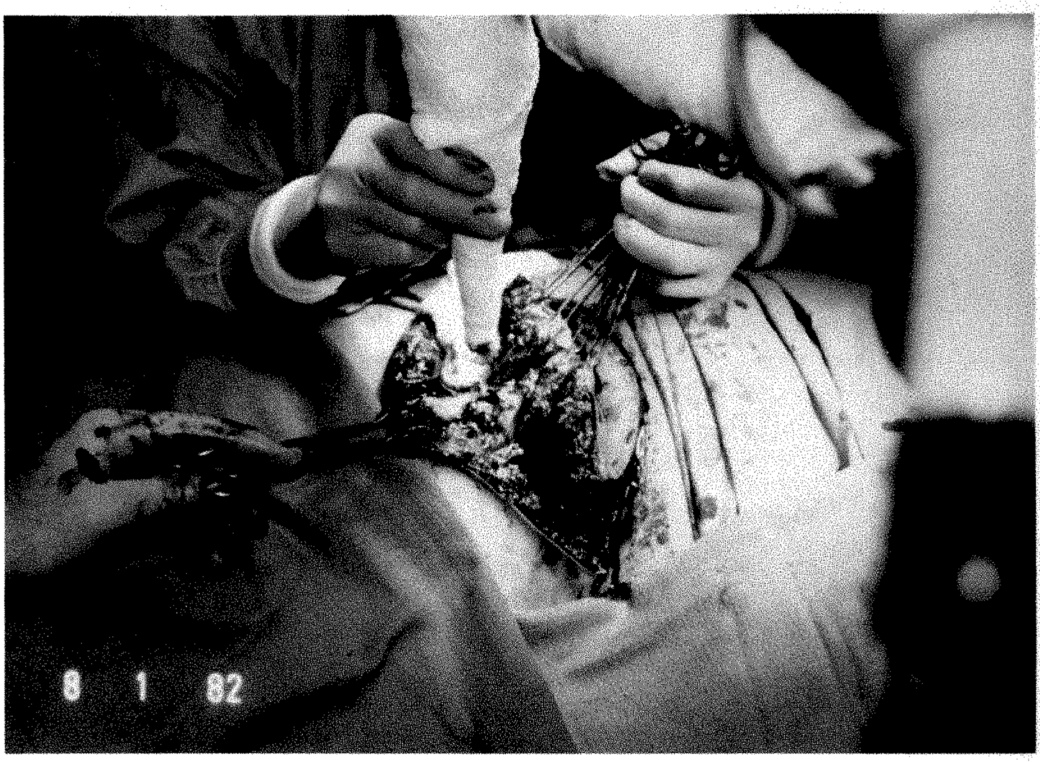


FIG. 5. Vascular infiltrative neurofibroma of abdominal wall being excised with CO_2 laser (center, gauzed-wrapped). Two previous attempts with conventional excisional methods failed due to severe hemorrhage.

ered. Goldman observed a group of human volunteers subjected to repeated low power argon cutaneous applications; no tumor formation was noted.[40] Apfelberg et al. carried out an *in vitro* study of fibroblast cultures irradiated with argon laser; no mutagenic effects were observed.[41]

Clinical Applications

Current clinical applications of lasers in general surgery are presented in two sections. The first section deals with conventional incisional surgical access laser techniques. The second section deals with the vast and rapidly growing endoscopic access laser surgical techniques, or minimally invasive endoscopic gastrointestinal laser surgery.

Coagulation and Excisions of Masses and Tumors

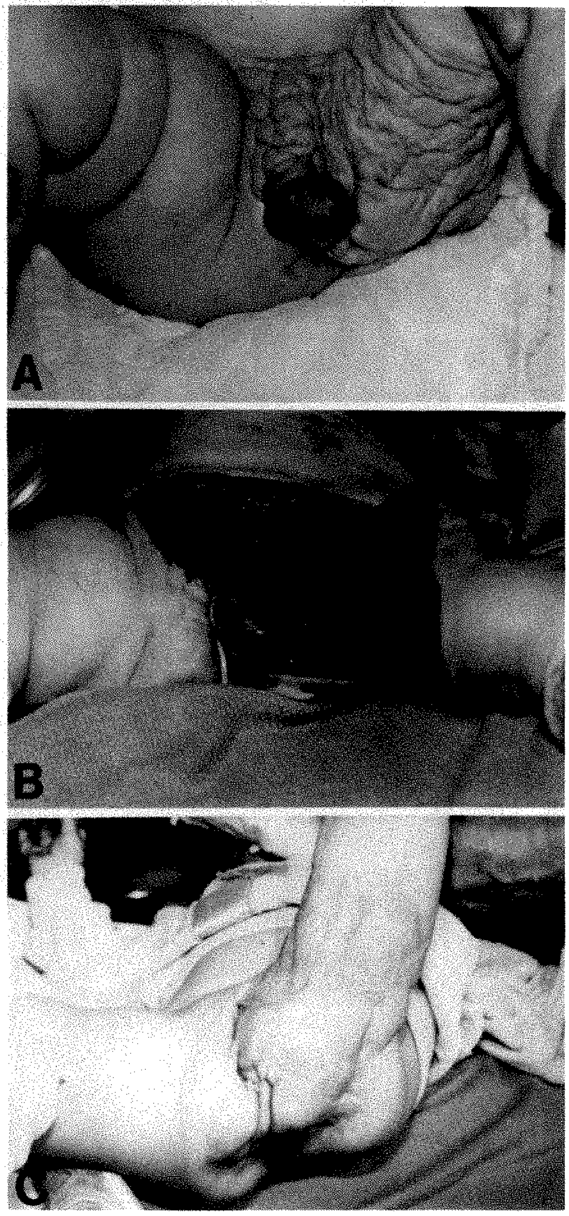
With its rich vascular supply, the tongue has been a difficult organ for the general surgeon to incise using standard techniques. With masses that are rather small and localized, excision with the CO_2 laser may be accomplished quickly and with minimal blood loss.[42] Due to rapid reparative processes of the tongue, thermal injury of laser does not result in significant delay in healing.

A conservative palliative application for control of vascular lesions of the tongue with lasers is being utilized. Argon and Nd:YAG lasers have been used effectively in a palliative fashion to reduce bleeding and size of such lesions without loss of functional tongue mass in 13 patients. A spot coagulation technique without cutting or vaporization is employed (Fig. 4). This has resulted in reduction of bleeding and lesion size for periods of up to 3 years. Retreatment has been required as symptoms recur.[43]

The CO_2 laser has been used effectively to treat leukoplakia and lesions of the oral mucosa. The unique superficial vaporization of this laser allows for a precise microsurgical removal of the dysplastic tissue. If the lesions are extensive, resultant ulcerations may require several weeks to heal completely and be quite uncomfortable for the patient. The recurrence rate, however, is much less than that with other techniques.[44]

Excision of vascular lesions of the scalp may likewise be facilitated with use of the CO_2 laser. Smaller vessels in the skin may be readily photocoagulated and larger vessels exposed. These vessels can be controlled by clips, ligature, or electrocoagulation. The bed in such excisions readily accepts a graft without delay in graft take or healing.[45] Similar vascular lesions of the trunk, abdominal wall, and extremities may be excised with reduced blood loss (Figs. 5 and 6).

A number of reports indicate facilitation of excision of head and neck tumors with the CO_2 laser, indicating better exposure, less blood loss, and decreased operating time.[46] A more specific application was outlined by White and Adkins for excision and vaporization of lym-



FIGS. 6A–C. *A.* Lymphangiosarcoma in 3-week-old female infant. *B.* Immediately following excision with CO_2 laser; 120 mL blood loss. *C.* Two years following skin graft, no recurrence. External genitalia preserved.

phangiomas of the head and neck in children.[47] Multiple thin-walled small extensions of the tumor that were difficult to excise were ablated by a handheld CO_2 laser technique.[47]

Breast

Considerable experimental and clinical study has been made of the carbon dioxide laser in treatment of carcinoma of the breast. Lanzafame et al. compared local tumor recurrence following scalpel, electrocautery, and laser excision of R3230AC mammary tumors in rats.[48] A statistically significant ($p < 0.05$) reduction in recurrence was noted with laser excision as compared with scalpel excision.[48]

In a controlled trial involving 209 patients, Ansanelli compared CO_2 laser excision and scalpel excision of breast malignancies.[49] Transfusions required, postoperative wound drainage, and hospital stay were all less for inpatients where CO_2 excision was performed.[49]

Recurrent breast cancer in the thoracic wall with necrosis and ulceration is a difficult surgical problem. Hira et al. utilized CO_2 laser and vaporization for excision of such tumors with reduction in blood loss and local infection. In a 2-year follow-up, however, no difference in rate of local recurrence between the control or treated groups was noted.[50]

Abdomen

Stomach

The Nd:YAG laser is frequently used in Russia for excision of gastric lesions with a report of decreased infection and blood loss. Special devices have been constructed to allow uniform circumferential transsection of stomach and intestine. It is suggested that there is better sterilization, less tissue turn in, and reduced anastomotic complications using this technique.[51] Hira and Moore employed similar contact techniques in 30 intraabdominal anastomotic procedures and stated that the laser did not damage intestinal margins as much as other methods, and was especially useful in excising inflammed vascular neoplastic tissue.[52]

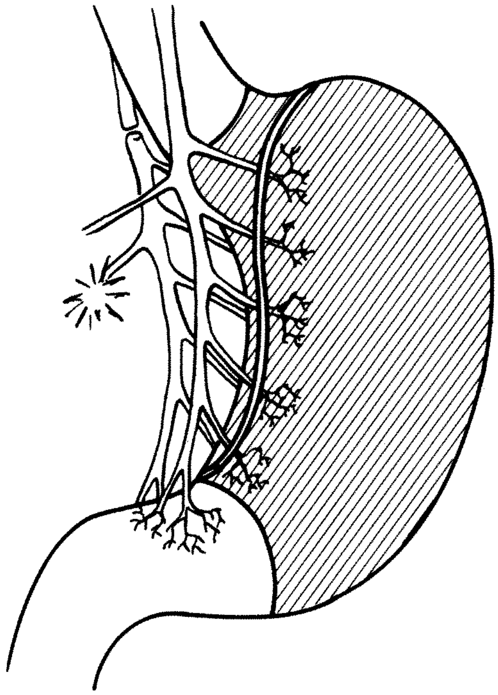


FIG. 7. Experimental laser vagotomy. Posterior truncal vagotomy followed by division of branches of anterior vagus along lesser curvature to nerve of Latarjet with either adjacent spot application or continuous sweep application of argon laser.

An unusual experimental gastric application has been suggested by Hunter et al. utilizing the argon laser plus vagotomy in dogs.[53] In this procedure, the posterior vagal trunk is divided. Following this, a laser myotomy is performed applying the argon laser along the anterior curvature from gastroesophageal junction to the nerve of Latarjet coagulating serosa and muscularis leaving muscosa intact. This procedure is designed to interrupt both the extramural and intramural branches of the left vagus nerve. Secretory studies indicating marked reduction in secretion are encouraging (Fig. 7).[53]

Pancreas

Excision of the pancreas has been performed using Nd:YAG laser in both experimental and clinical situations.[54] Donna utilized the Nd:YAG laser in order to preserve the duodenum with its blood supply in canine surgical procedures.[55] A statistically significant reduction in operating time and blood loss was reported.

Liver

The liver was early suggested as a site for laser applications for hemostasis or sublobar excisions.[56] Laboratory studies indicate that it is feasible to excise portions of the liver with CO_2 or Nd:YAG laser. Schroder et al. employed contact tip Nd:YAG excision combined with a flexible plastic strapper for canine liver resections with reduction in operating time and blood loss.[57]

It appears, however, that the present lasers may be most useful for hemostasis involving large oozing surfaces of the liver due to trauma. Standard surgical techniques will likely continue to be utilized in elective lobar resections to control major vascular and biliary structures. Sublobar resections and vaporization of scattered hepatic metastases, especially in tumors of endocrine origin, may be facilitated by the use of lasers.

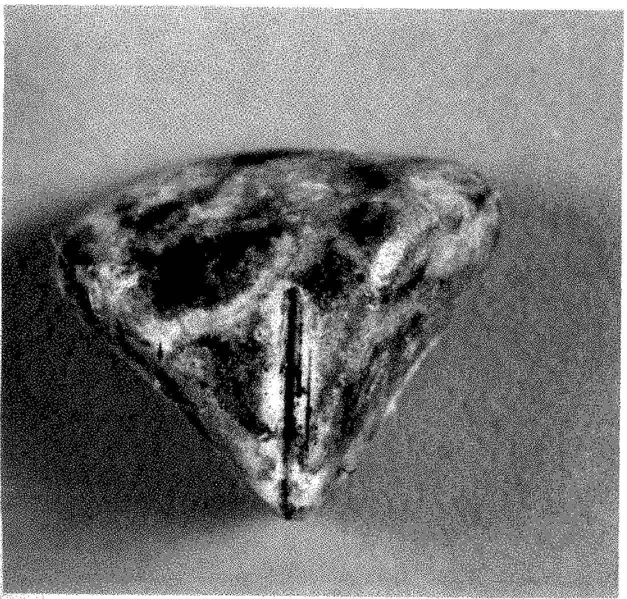
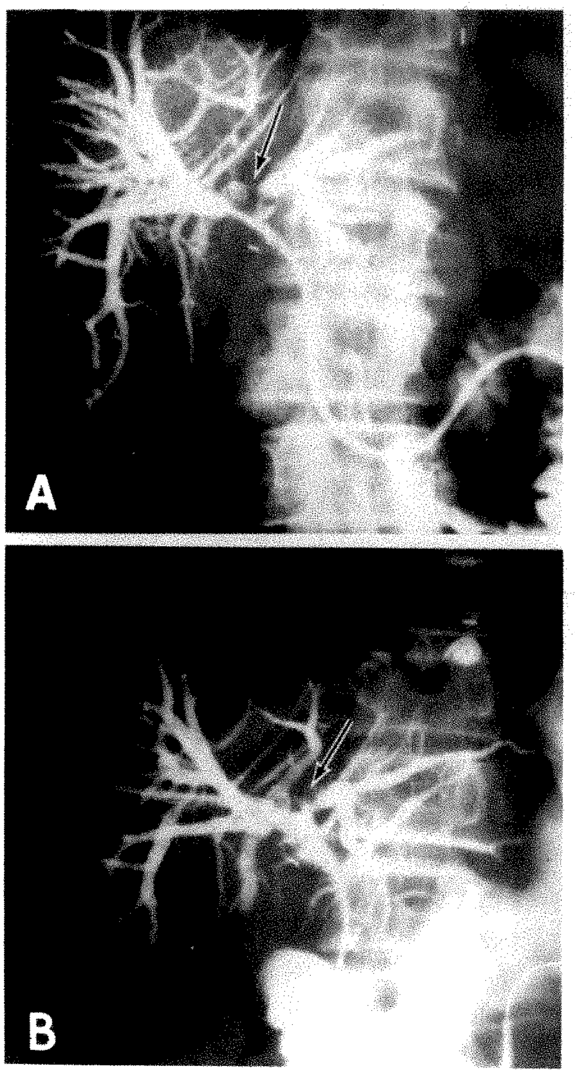


FIG. 8. Mixed calcium cholesterol pigment stone. Central incision made with free electron laser at 2.9 μm wavelength. Small incision on stone to right of center 20 μm width. No evidence of thermal damage.



FIGS. 9A and B. *A*. Cholangiogram of patient with Klatskin tumor. A percutaneous tube is draining the right hepatic duct system. The left remains obstructed (arrow). *B*. The same patient following endoscopic laser treatment of tumor required to control hemorrhage. The left hepatic duct system is no longer obstructed (arrow).

Biliary

Biliary calculi can be fragmented and removed using the Nd:YAG laser. The laser is guided by endoscopic means using a transampullary, percutaneous transhepatic, or tube tract approach.[58] Pigmented and mixed stones are readily reduced to smaller pieces. Pure cholesterol stones or heavily calcified stones are more difficult to reduce. Fragmentation is achieved by placing a fiber in contact with the stone and applying repeated brief impulses. Stones may then be removed by catheter or by grasping forceps. This technique may be especially

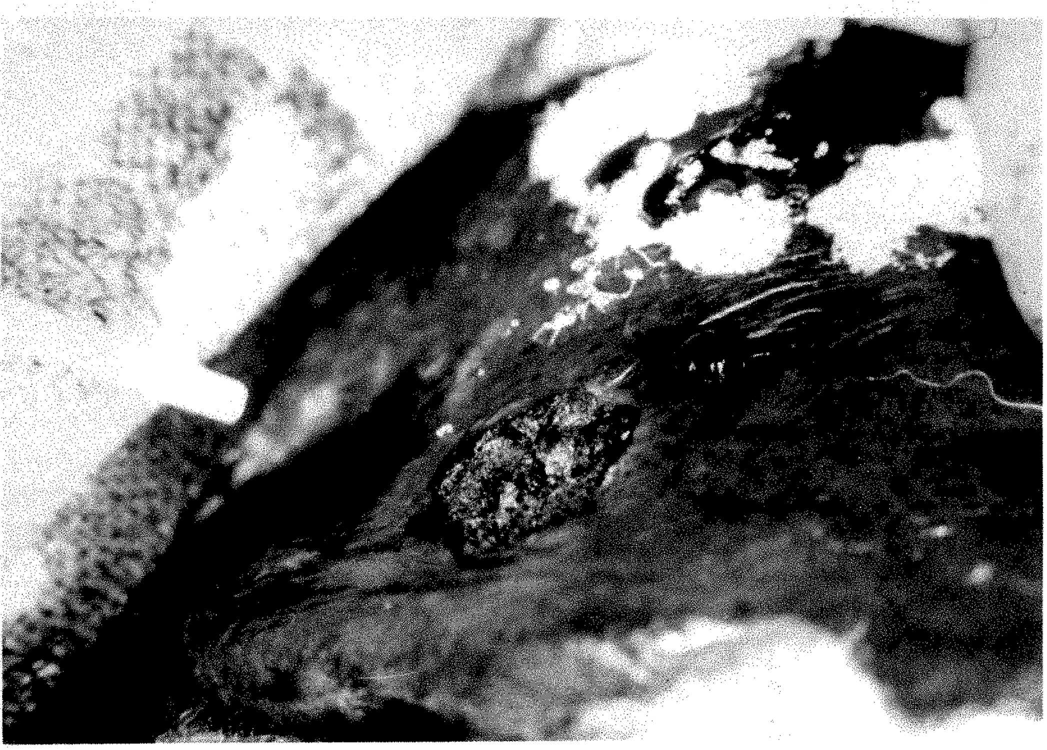


FIG. 10. Superficial capsular injury of spleen. Bleeding through microfibrillar collagen (*top*). Control of bleeding with multiple application of Nd:YAG laser, fiber at left (*bottom*).

useful in retained intrahepatic stones that cannot be removed by conventional techniques.[59]

A major problem with gallstone fragmentation with the Nd:YAG laser is the generation of heat that can damage biliary mucosa. The recent introduction of the flash lamp pumped dye (400–750 nm) laser for fragmentation of urinary calculi suggests this same technology may be applicable to biliary calculi.[60] The exact mechanism of stone fragmentation by this technique is not fully defined but may result from plasma formation and with photomechanical disruption. Dayton and Dixon measured *in vitro* thermal effects of gallstone fragmentation with Nd:YAG, copper vapor, and flash lamp pumped dye lasers.[61] Significant peripheral temperature elevations were noted during fragmentation with Nd:YAG and copper vapor but not with flash lamp pumped dye laser.[61] The free electron laser was utilized to photoablate gallstones by Dixon et al.[62] This high energy pulsed device allows precise incision and reduction in size of stone with minimal thermal effects (Fig. 8). These devices, possibly combined with ultrasonic fragmentation, suggest a future role for laser applications especially for intrahepatic, retained common duct calculi, and possibly even gallbladder stones.

A unique hepatobiliary endoscopic application of the laser involved percutaneous transhepatic insertion of an endoscope into dilated biliary radical above bleeding intrahepatic bile duct tumors. Utilizing the Nd:YAG laser fiber through a pediatric bronchoscope, bleeding from a Klatzkin tumor was controlled and symptomatic relief from obstruction provided (Fig. 9).[63] The Nd:YAG laser has also been used for endoscopic papillotomy where conventional techniques have failed.

Spleen

The Nd:YAG laser has been found to be effective in controlling experimental superficial splenic capsular bleeding (Fig. 10). Larger central vessels cannot be controlled with the laser. A technique has been described for segmental or partial splenectomy involving ligature of selected hilar vessels and Nd:YAG vaporization of splenic capsule, superficial sinusoidal tissue, and smaller peripheral vessels. Coagulated material is aspirated. As the hilum is approached, vessels larger than 1 mm are skeletonized, clipped, or suture-ligated. (Fig. 11).[64]

Anal and Regional

Laser hemorrhoidectomy is reported with increasing frequency but still remains controversial. The CO_2 laser is used in some techniques in conjunction with standard surgical ligation and excision. The laser is reported to be effective in elevating mucosal flaps with preservation of anoderm and reduction in pain.[65,66]

Sankar and Joffe devised a new technique of hemorrhoidectomy utilizing a Nd:YAG with contact tips as an excisional method.[67] A limited clinical trial indicated less blood loss, pain, urinary retention, and fewer healing complications as compared with conventional techniques.[67]

The removal of condylomata of the perianal region may be accomplished with CO_2, argon, or Nd:YAG lasers.[68] With all wavelengths, it is essential to remove all epidermis for at least 1 cm surrounding any active lesion since virus has been found in prickle cells for at least that distance. If the brush technique described by Baggish is not employed, the recurrence rate is much higher.[69]

Since live virus may be disseminated in the air during condylomata vaporization, gloves, masks, gowns, and other precautions are essential.[70]

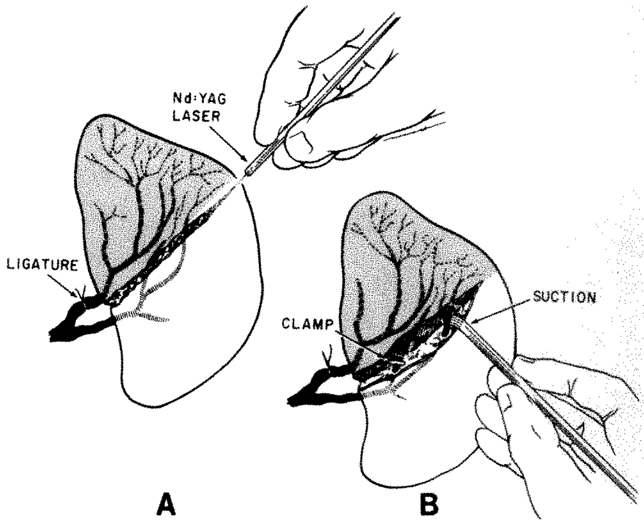
Pilonidal Cystectomy

CO_2 excision of pilonidal cyst has been reported. The hemostatic and bacteriocidal effects of the laser are utilized in tracing out and excising, or vaporizing, the numerous tracts of this troublesome lesion.[71]

Decubitus Ulcer

Excision of decubitus ulcers with the CO_2 laser has been described in reports of treatment of several thousand patients.[72] The ability of the laser to vaporize infected tissue is used, which allowed earlier grafting of the exposed site.

A controlled trial of laser *versus* conventional ulcer excision involving 66 patients was conducted by Juri et al.[73] Statistically significant differences in favor of the laser-treated groups were noted in operative blood loss, infection rate, and recovery rate. The sum of these factors resulted in a mean of 23 fewer hospital days per excisional procedure in laser-treated patients as compared with control patients (Fig. 12).[73]



FIGS. 11A and B. *A.* Ligation of segmental vessel with photocoagulation of capsule and parenchyma using Nd:YAG laser. *B.* Skeletonizing of large vessels in dry field using neurosurgical sucker. Clips applied followed by transection of vessels and completion of procedure with laser.

Infected Wounds

Primary closure of phlegmons, abscesses, and carbuncle following total excision with CO_2 laser was reported

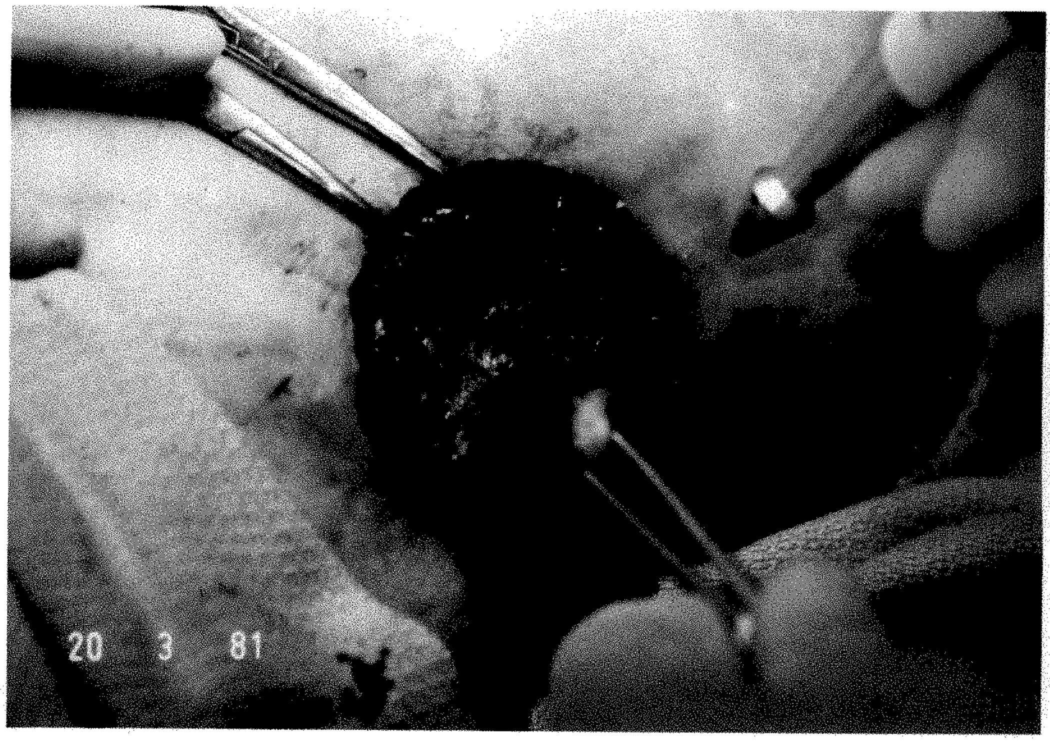


FIG. 12. Excision of decubitus ulcer with CO_2 laser. Necrotic base has been vaporized followed by circumferential excision of entire ulcer and bed (CO_2 laser handpiece, *upper right*).

TABLE 1. *Endoscopic Laser Treatment of Surgical Disease*

Oral leukoplakia
Lingual vascular lesions
Esophageal diverticulum
Esophageal web
Esophageal varices
Barrett's esophagus
Esophageal cancer (palliation)
Sutures, foreign bodies, granulomas
Mallory-Weiss syndrome
Gastric polyps
Gastric varices
Gastric telangiectasia, AVM
Peptic ulcer, hemorrhage
Gastric carcinoma, palliation
Gastric carcinoma, early, control
Duodenal leiomyoma
Duodenal carcinoma, palliation
Hepatic bile duct carcinoma
Hepaticolithiasis
Choledocholithiasis
Stricture of hepatic duct
Pseudocyst of pancreas
Ampullary stenosis
Carcinoma of ampulla
Polyps and AVM, intestine
Colon vascular lesions
Colon polyps
Colon cancer, palliation
Radiation proctitis, hemorrhage
Endometriosis, colon
Anastomotic strictures, stenosis, adhesions
Suture granulomas
Postsurgical anastomotic bleeding

by Chegin et al.[74] Tube drainage was frequently utilized; of 247 patients so managed, 233 did not require further incision or drainage.[74]

Endoscopic Gastrointestinal Laser Surgery

Remarkable advances in the endoscopic approach to intraluminal (and selected extraluminal) GI lesions have been made. Newer endoscopic devices provide excellent visualization of mucosal or submucosal lesions with ample operative channels for introduction of laser fibers or a variety of electrosurgical or heater probes. A partial list of endoscopic GI laser surgical procedures employed for treatment of general surgical disease processes appears in Table 1. Space limitations allow only briefest mention of representative applications in acute GI hemorrhage, vascular malformations, small benign mucosal lesions, GI malignancy, cysts, and stenoses.

Gastrointestinal Bleeding

A summary is available of nine prospective controlled randomized studies of endoscopic laser treatment of patients with acute upper GI hemorrhage (mostly peptic ulcers).[75] Three of the studies failed to show significant differences in long-term hemostasis or requirements for surgery or survival, although initial hemostasis was achieved in approximately 90% of laser-treated patients. A study by Rutgeerts et al.,[76] which included the largest number of patients, however, showed a statistically significant decrease in rebleeding rate, necessity for urgent surgery, and reduction of mortality rate in laser-treated patients. Laser therapy for active GI hemorrhage appears to be beneficial only in patients with actively bleeding peptic ulcer disease or with nonbleeding visible vessels in an ulcer crater. Lesions such as diffuse gastritis and those inaccessible endoscopically are not suitable for laser therapy.

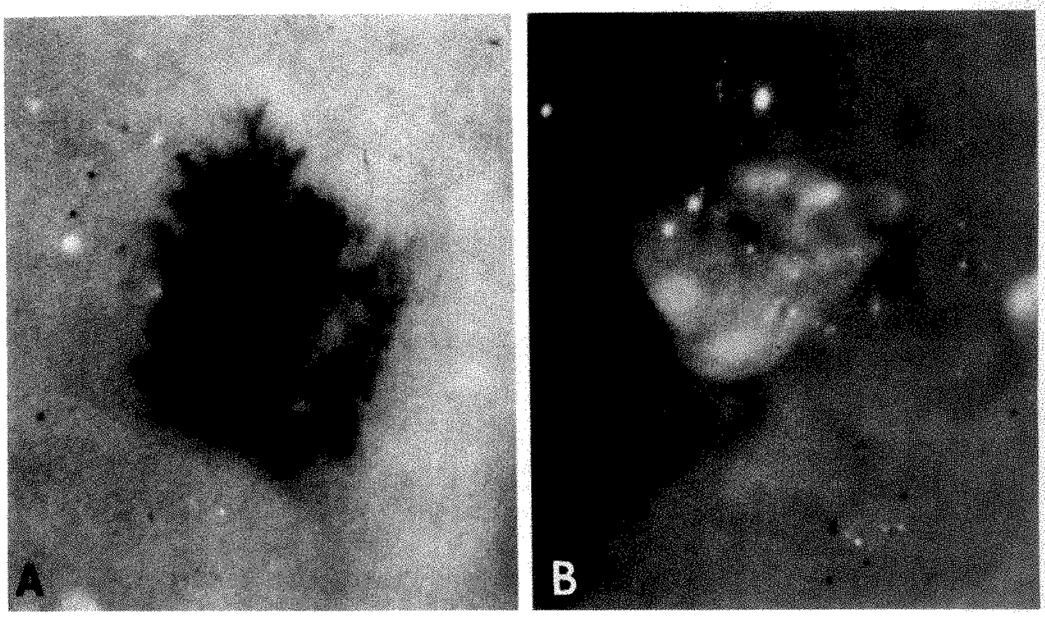
One of the greatest indirect contributions of the laser for endoscopic therapy has been the requirement for precise early identification of the bleeding lesion. This has resulted in new visual management criteria based upon the presence or absence of spurting lesions, visible vessels, or stigmata of recent hemorrhage.[77] Massively bleeding arterial lesions are recognized early and referred for surgery without further delay. Endoscopic laser conversion from bleeding to stabilized patients, even for a brief period of time, may assist the surgeon in management of these difficult problems.

Vascular Malformations

These lesions are particularly suited to laser therapy since they are frequently limited to the mucosa or submucosa and heavily absorb light in the argon range (Fig. 13). The combined experience at the Universities of Utah and Lille now includes 80 patients with upper GI, 26 with colonic, and nine patients with upper and lower vascular lesions. Twenty had Osler-Weber-Rendu (OWR) syndrome. The overall results in these patients were similar to other reports with over 95% success in controlling blood loss in patients with sporadic vascular malformations and reduction in frequency of bleeding in patients with the OWR syndrome.[78] No perforations or major complications occurred. Rutgeerts et al. reported the treatment of 482 GI vascular lesions in 59 patients with Nd:YAG laser.[79] Overall results were good with only 17 patients rebleeding.[79] Buchi followed 44 patients for up to 3 years following laser treatment of vascular malformations and found a statistically significant reduction in frequency of bleeding, transfusion rates, and requirement for surgery.[80] The collective experience of various centers indicates that laser treatment of GI vascular malformations is safe and effectively terminates or markedly decreases frequency of bleeding.

Small Multiple Benign Mucosal Lesions

Dixon et al. studied endoscopic argon laser treatment in 34 patients with Gardner's syndrome with multiple polyps in residual rectum following subtotal abdominal colectomy.[81] Over 1100 polyps were removed without



FIGS. 13A and B. *A*. A 5-cm diameter superficial hemangioma of lesser curvature of the stomach with recurrent bleeding. *B*. Immediately following argon laser photocoagulation of hemangioma. No recurrence after 3 years follow-up.

complication (Fig. 14). A similar experience was noted by Brunetaud et al. at the University of Lille.[78] Other lesions successfully treated include gastric polyps, endometriosis coli, and localized lesion in Barretts' esophagus. The laser should not be used to remove pedunculated polyps since there is usually a central vessel that is difficult to control without the constrictive effects possible with electrocautery snares.

Villous Adenoma

The management of villous adenoma is more controversial. Lambert and Sabben reported complete laser destruction of 35 of 39 villous adenomas, with reduction of size of lesion in the remainder; four perforations were noted, but two did not require treatment.[82] Brunetaud recently reported treatment of 109 villous adenomas in this fashion; 19% had local recurrence, but all were successfully ablated with repeated laser treatment.[83] Five patients with invasive carcinoma were discovered in the course of treatment and referred for surgery.[83]

Gastrointestinal Malignancy

Palliative therapy of GI malignancy is one of the more appealing applications of endoscopic laser surgery. Neoplasms of the esophagus, stomach, duodenum, hepatobiliary tract, colon, and rectum have been managed in this fashion for control of bleeding, relief of obstruction, management of secretions, or to allow oral nutrition (Fig. 15).[84] Applications have been made in lesions that are incurable by surgical resection, recurrent lesions, in patients who cannot withstand a surgical procedure, or in preparation of a patient for surgery. Laser procedures have the advantages that they can be carried out with minimal or no sedation and generally on an outpatient basis, with potential reduction in complications, medical costs, and hospital stay.

Fleisher and Sivak[85] treated 68 patients with esophageal cancer with the Nd:YAG laser who were not candidates for surgery or radiation therapy, with relief of dysphagia in 92% and clinical improvement lasting 3–6 months. Five patients (12%) developed tracheoesopha-

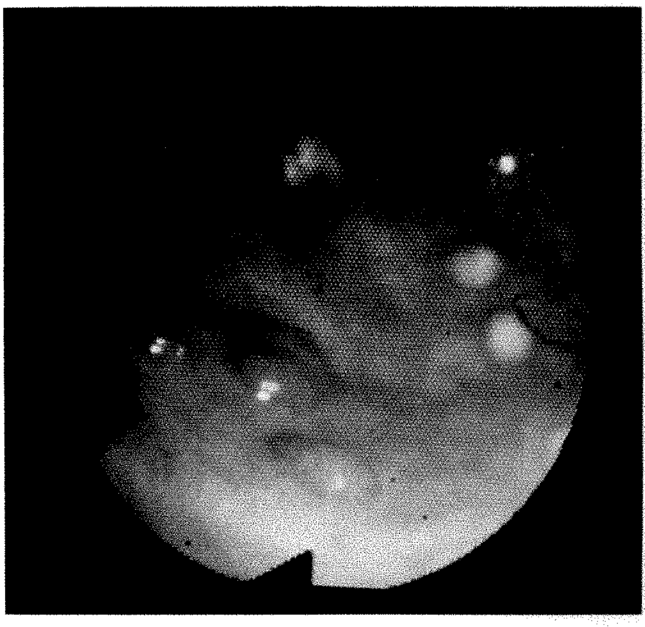


FIG. 14. Multiple polyposis of colon (Gardner's syndrome). Untreated polyps (*below*). White coagulated polyps treated with argon laser (*above*).

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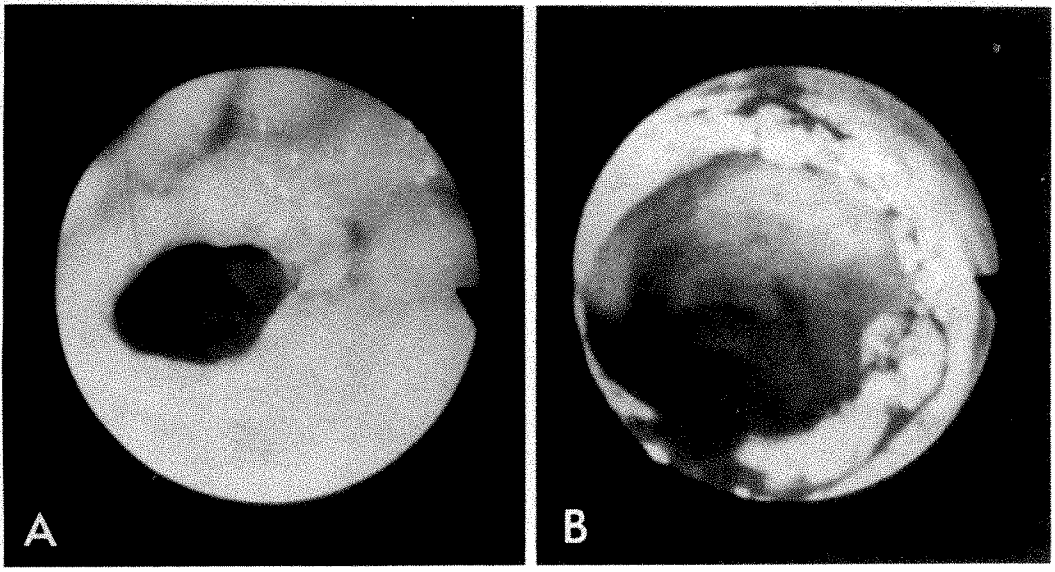


FIGS. 15A and B. *A.* Stenosis of low rectal anastomosis with recurrent malignancy at suture line in patient with distal metastases. *B.* Immediately following Nd:YAG incision of stenosis and vaporization of tumor. Patient died 13 months later without recurrence of stenosis or local tumor.

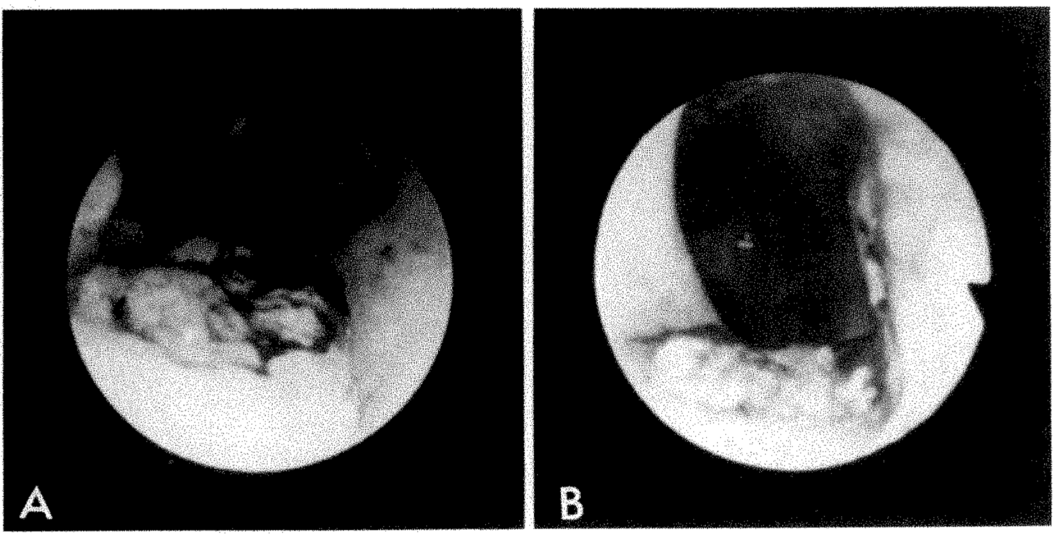
geal fistulae or perforation. Two of these were clearly laser-related, but the other three occurred up to 6 months after laser treatment. Patients managed in this fashion required retreatment as progression of the growth occurs.[85] As would be expected, no increased length of survival was noted.

Gastric and distal esophageal malignancy may be managed by endoscopic laser therapy with similar results. Thirty-four patients were treated at the University of Utah Laser Institute; 91% of patients were relieved of gastric or distal esophageal obstruction and 2% developed fistulae.[78]

In a cooperative study 118 patients were treated for surgical preparation or palliation of colorectal malignancies at the University of Utah and the University of Lille. Control of bleeding or relief of obstruction with the Nd:YAG laser was possible in all patients (Fig. 16). An average of three initial treatment sessions was required. Few complications were encountered.[78] Again, retreatment was necessary as tumor growth progressed.

Endoscopic Incisional

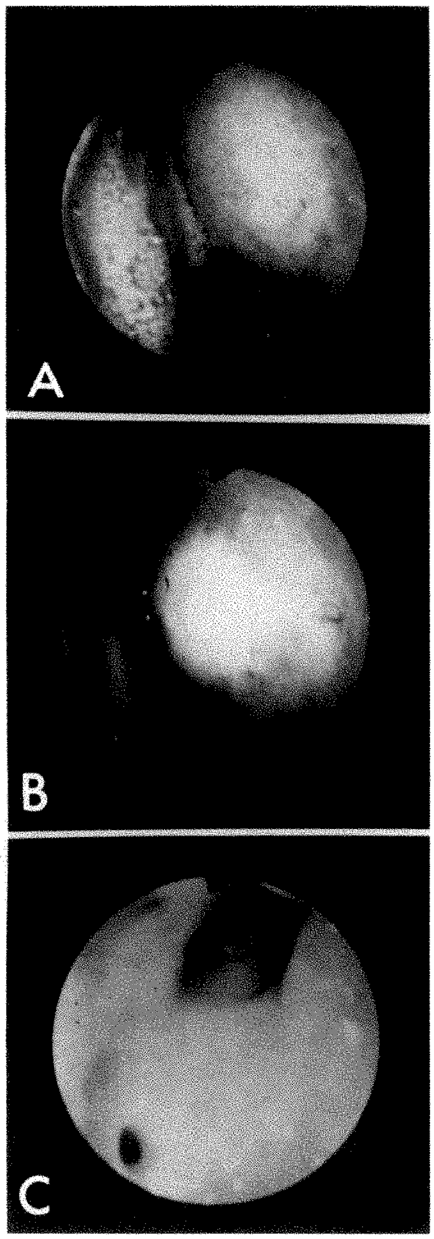
Increasing experience with endoscopic surgery has resulted in unique applications involving endoscopic incisional methods. This has been facilitated by the development of contact tips for laser fibers, which allow for precise laser application to such lesions. Potential procedures of this type are limited only by visualization of the lesion and endoscopic skills of the surgeon. Delmotte et al. utilized the argon laser to drain pancreatic and biliary cysts internally.[86] Buchi et al. employed the Nd:YAG laser to drain two symptomatic expanding



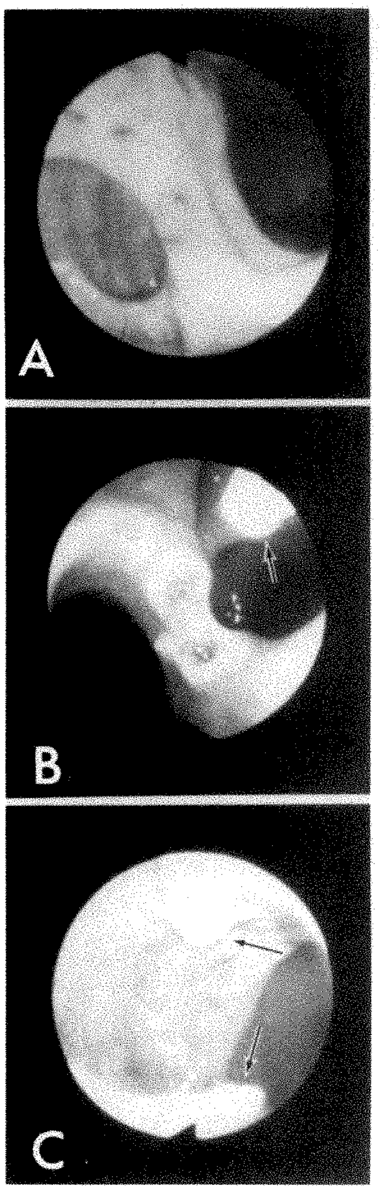
FIGS. 16A and B. *A.* Cancer of rectum with acute bleeding. *B.* Immediately following Nd:YAG endoscopic photocoagulation with control of bleeding. Patient was then treated surgically on elective basis.

traumatic pancreatic pseudocysts in patients who could not undergo operative cystogastrostomy.[87] An area of the gastric wall overlying the pseudocyst was heavily photocoagulated, and subsequent slough created a large pseudocystogastrostomy. No recurrence of cysts was noted in a 3-year follow-up (Fig. 17).[87]

A number of reports have described the use of lasers for successful incision and enlargement of postoperative stenosis of the esophagus and colon.[88] Peptic strictures, congenital rings, and postoperative webs have likewise been incised and dilated (Fig. 18).[89] Innovative incisional applications are in the early investigative phase but promise to greatly influence the practice of GI surgery.



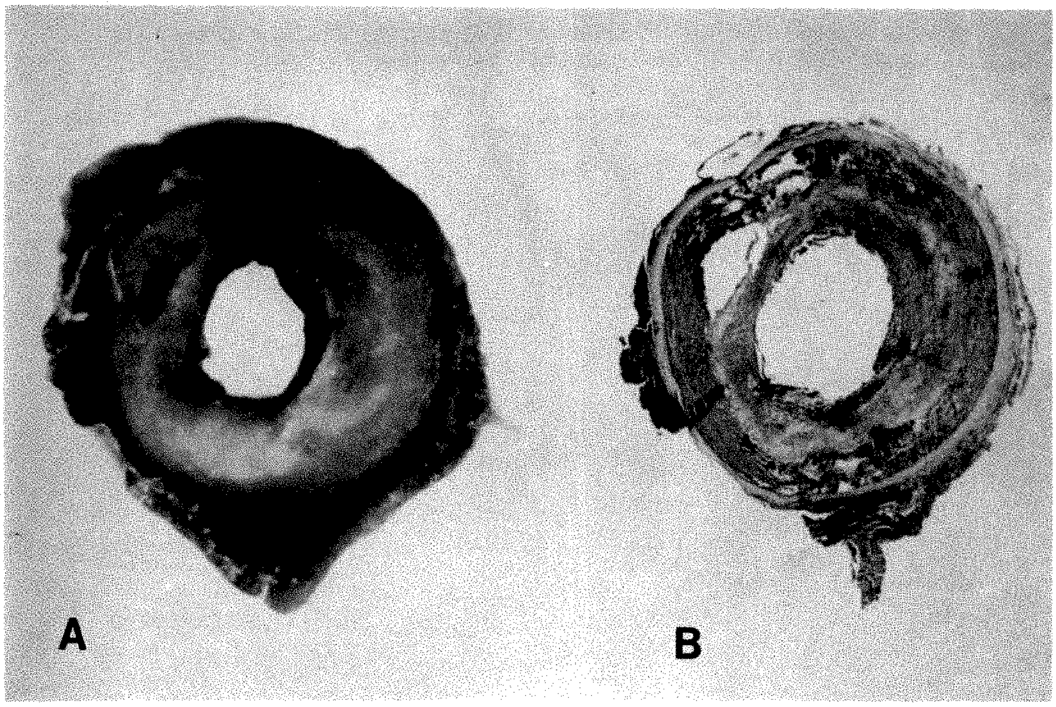
FIGS. 17A–C. *A*. Displacement of posterior wall of stomach in critically ill patient with traumatic pancreatitis and pseudocyst, right. *B*. Immediately following endoscopic Nd:YAG photocoagulation of gastric wall and anterior wall of cyst. *C*. Five days following treatment with slough of gastric wall and wall of pseudocyst with effectively functioning pancreaticocystogastrostomy with drainage of cysts. No recurrence.



FIGS. 18A–C. *A*. Intraluminal side-to-side adhesion following ileal J-pouch construction with malfunction. *B*. Argon laser endoscopic division of vascular adhesion. Laser fiber (arrow). *C*. Immediately following argon laser division. Note that good retraction of adhesion ends with no bleeding.

Vascular

Lasers have been employed experimentally and clinically in microvascular welding and recanalization of atherosclerotic vessels. In microvascular welding, vessels of 1 mm in diameter or less are joined using spot weld



FIGS. 19A and B. *A.* Autopsy specimen of atherosclerotic femoral artery. *B.* Immediately following argon laser vaporization of atheroma. Note the increase in luminal diameter but thermal injury, arterial wall.

techniques or by application of external supports of laser-coagulated collagen or blood.[90] Such techniques appear to reduce foreign body inflammatory action, preserve normal vascular anatomy and luminal diameter, and allow growth of vessels without stenosis, which may be particularly advantageous in children.[91]

The ability to transmit laser energy through small flexible fibers has suggested application use for recanalization of occluded atherosclerotic arteries by catheter or endoscopic techniques.[92] *In vitro* studies have shown that atherosclerotic plaque can be vaporized with various lasers, especially where the chief component is cholesterol (Fig. 19).[93] Calcified plaque is more difficult to ablate, however.[94] Several preliminary case reports are available utilizing either Nd:YAG or argon laser to recanalize occluded femoral arteries. Vessels in 16 patients studied in one series were recanalized with two perforations. No major hematomata occurred despite full anticoagulation with heparin.[95] In another series of 51 attempted femoral artery procedures using a thermal laser tip, nine were immediate failures due to either inability to recanalize the lesion or to thrombosis. Initial patency rate of 83% slowly dropped to 73.2% at the end of a 21-month period.[96]

Due to injury and perforation of arterial wall, selective ablation of plaque with or without the use of exogenous photosensitizers seems vital before advances can be made. The effect of the debris created by vaporization of plaque on the peripheral vascular bed has been studied and appears to be minimal in extremities.[97] The effect of such debris on critical peripheral beds such as brain, kidney, and myocardium have not been fully studied.

Photodynamic Therapy

Photodynamic therapy (PDT) is a new procedure involving known photobiologic principles that may be useful in the treatment of various tumors and disease processes.[98] Current laser applications depend upon absorption of laser energy by naturally occurring molecules in tissue such as hemoglobin or melanin (endogenous chromophores). It has been known since 1903 that various drugs could be introduced intravenously that would bind selectively to tumors or associated vascular beds.[99] Hematoporphyrin derivative (HPD) has been one of the agents most widely studied in this regard.[100] After a period of 24–48 hours after injection, much of the photosensitizer (HPD) is cleared from normal cells and organs but is retained in high concentrations in tumors, plaque, inflammatory tissue, and certain bacteria. After the clearing period, light of appropriate wavelength to activate the sensitizer is applied directly to the tumor by an interstitial fiber or by endoscopic techniques. While some thermal reaction may occur, this is minimal. The chief effect of the photosensitizer is to initiate a chemical reaction in target cells, which results in fluorescence and the formation of singlet oxygen with associated phototoxicity and selective tumor damage (Fig. 20).[101]

Much of the initial clinical work using photosensitization has been carried out in recurrent carcinoma of the breast with cutaneous metastasis. Carruth and Dougherty reported initial reduction in tumor size in 60–70% of patients so treated.[102] In carcinoma of the bronchus, Hayata et al. treated 35 patients with PDT where conventional surgery was not possible with good reduction in tumor mass or palliation reported in 30–40% of patients.[103] A summary of the literature of current clinical results appears in Table 2.

Another unique element in photosensitization is that photosensitizer can be activated to fluoresce when the appropriate wavelength light is applied (Fig. 21). This has been employed in the bronchoscopic identification of early tracheobronchial carcinoma.[103] These techniques might provide for early tumor diagnosis utilizing fluorescence followed by phototherapy to cause selective destruction of sensitized tumor cells.

TABLE 2. *Summary of Response of Various Tumors to PDT (to 1984)*

Tumor Type	No. of Patients or (Sites)	Response CR	PR	NR	Longest Follow-up to Date (yr)
Skin (met. breast, basal cell, squamous, melanoma)	(219)	(147)	(29)	(43)	4
Endobronchial					
Late stage	262	106*	136	20	1.5
Early stage	32	17	10	—	4.5
Bladder, superficial	(70)	(38)	(16)	(13)	2
Head/neck, recurrent	49	9	26	14	2
Gynecologic, recurrent	11	4	5	2	2
Esophagus, advanced	17	0	11†	6	1

CR = complete remission; PR = partial remission; NR = no remission.

* Complete opening to wall of lumen following physical removal after PDT.

† Partial relief of obstruction.

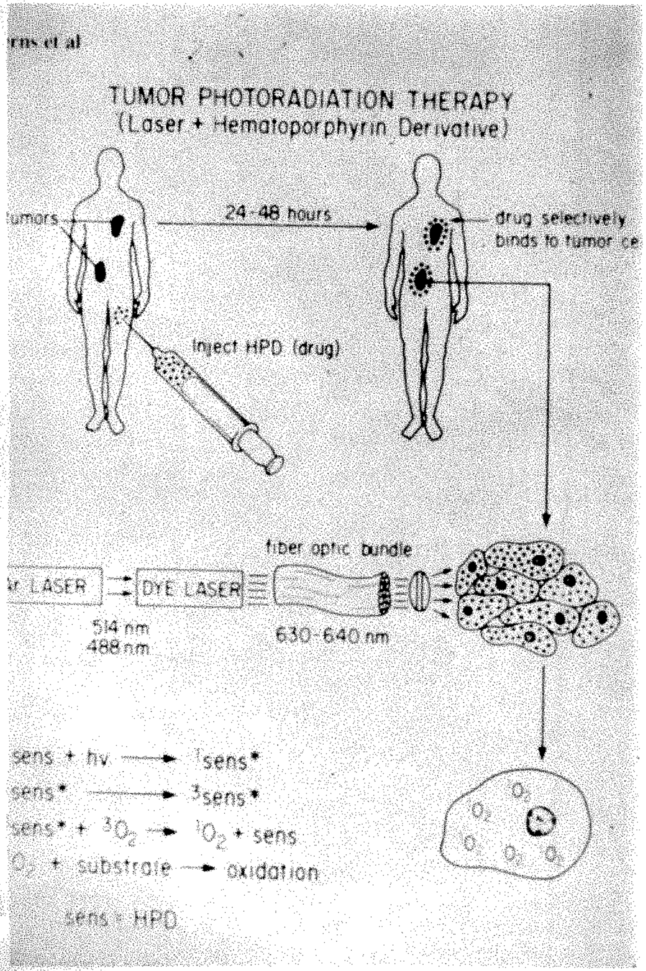


FIG. 20. Schema of PDT with hematoporphyrin derivative (after Dougherty).

Numerous new photosensitizers with greater potency and tumor selectivity are available and await appropriate preclinical studies and approvals.[104]

Discussion

The entire field of applications of lasers in general surgery is dynamic and evolving, and it requires constant critical evaluation. The field has been plagued by an inordinate amount of media attention and the usual plethora of uncontrolled enthusiastic reports by early investigators. Fortunately, well-designed trials are now becoming available to provide tenable guidance relative to indications and contraindications for application of these devices. At this point however, certain observations seem warranted:

1. Laser applications in general surgery now have achieved limited but defensible indications for certain selected procedures.
2. The use of lasers as a surgical instrument employed through endoscopes has resulted in a number of GI applications that will impact conventional incisional methods. It appears inevitable that the general surgeons of the future will need skills in at least upper GI endoscopy, colonoscopy, and choledochoscopy to utilize minimally invasive laser and other techniques.
3. The utilization of photosensitizers to identify by fluorescence and treat various tumors by phototherapy opens interesting possibilities for primary management or adjunctive treatment in association with conventional surgery.

Technologic advances promise smaller, less expensive, more reliable lasers with improved delivery devices for handheld operative microscopes or for endoscopic

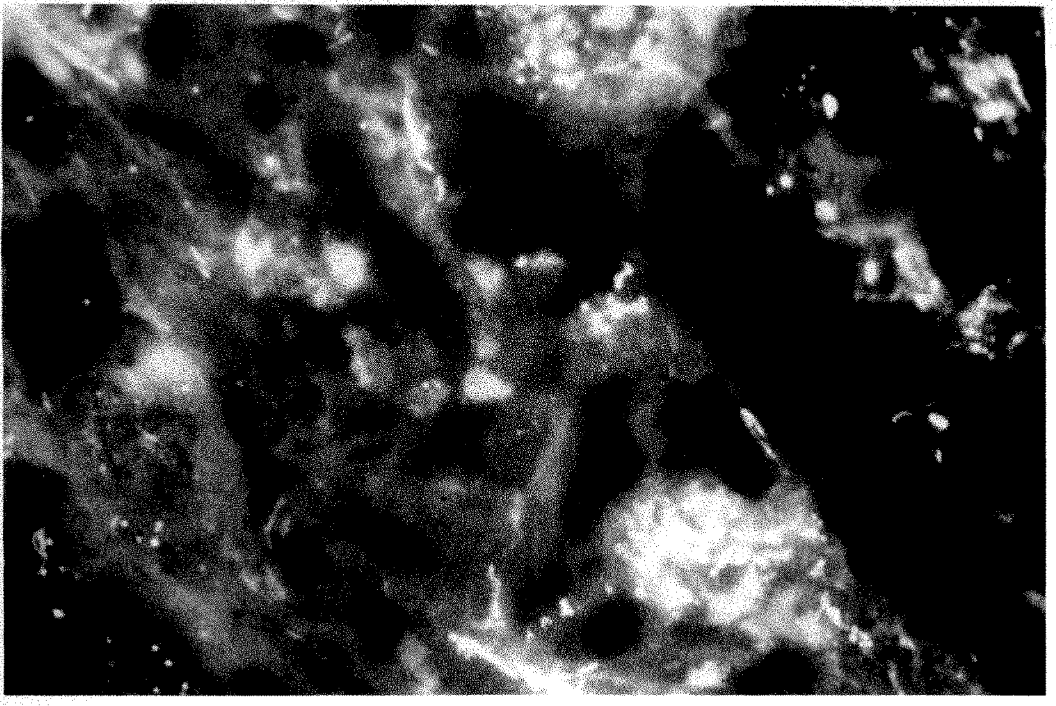


FIG. 21. Fluorescence of HPD-sensitized mouse tumor cells (scattered white spots) with 420 nm light; normal cells in background (dark areas).

use. New wavelengths and even tunable lasers will appear in the near future.

Despite the fact that membership in the American Society for Laser Medicine and Surgery recently passed the 1000 mark, not every surgeon should buy a laser. These expensive devices should be utilized only for specific indications where standard techniques are not available or are less efficacious. It is important, however, for every general surgeon to remain aware of developments in this field, which involve many new and intriguing aspects of photobiology and light tissue interactions that may prove to have surgical application.

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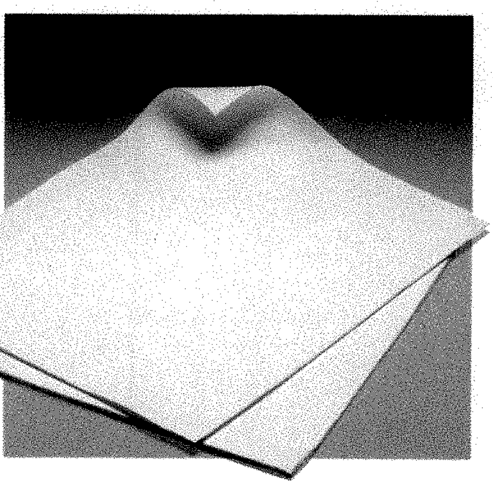

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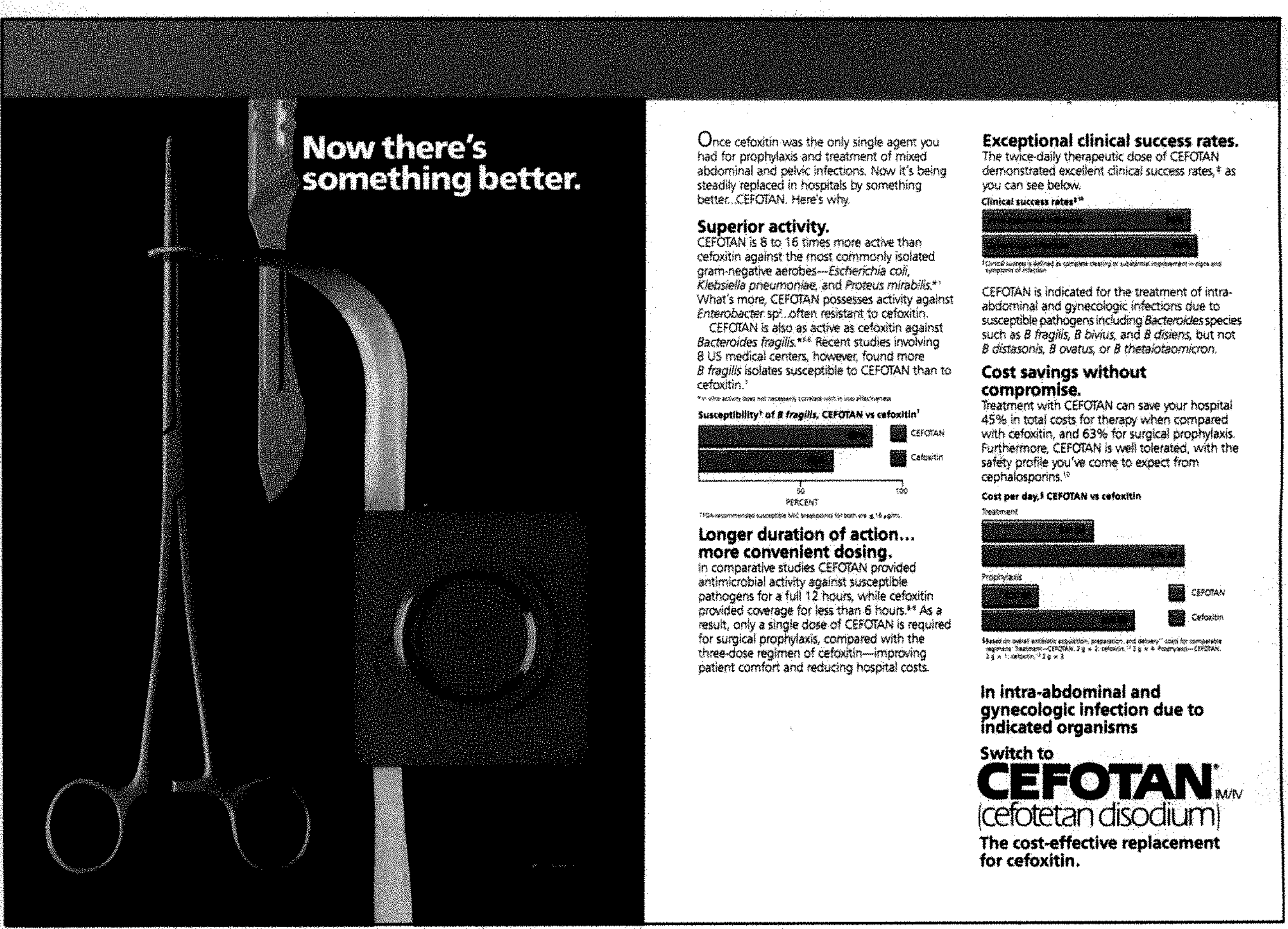

Now there's something better.

Once cefoxitin was the only single agent you had for prophylaxis and treatment of mixed abdominal and pelvic infections. Now it's being steadily replaced in hospitals by something better...CEFOTAN. Here's why.

Superior activity.

CEFOTAN is 8 to 16 times more active than cefoxitin against the most commonly isolated gram-negative aerobes—*Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*.*[1] What's more, CEFOTAN possesses activity against *Enterobacter* sp[2]...often resistant to cefoxitin.

CEFOTAN is also as active as cefoxitin against *Bacteroides fragilis*.*[3-6] Recent studies involving 8 US medical centers, however, found more *B fragilis* isolates susceptible to CEFOTAN than to cefoxitin.[7]

Susceptibility† of *B fragilis*, CEFOTAN vs cefoxitin[7]

CEFOTAN
Cefoxitin
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100
PERCENT

Longer duration of action... more convenient dosing.

In comparative studies CEFOTAN provided antimicrobial activity against susceptible pathogens for a full 12 hours, while cefoxitin provided coverage for less than 6 hours.[8,9] As a result, only a single dose of CEFOTAN is required for surgical prophylaxis, compared with the three-dose regimen of cefoxitin—improving patient comfort and reducing hospital costs.

Exceptional clinical success rates.

The twice-daily therapeutic dose of CEFOTAN demonstrated excellent clinical success rates,‡ as you can see below.

Clinical success rates‡[10]

CEFOTAN is indicated for the treatment of intra-abdominal and gynecologic infections due to susceptible pathogens including *Bacteroides* species such as *B fragilis*, *B bivius*, and *B disiens*, but not *B distasonis*, *B ovatus*, or *B thetaiotaomicron*.

Cost savings without compromise.

Treatment with CEFOTAN can save your hospital 45% in total costs for therapy when compared with cefoxitin, and 63% for surgical prophylaxis. Furthermore, CEFOTAN is well tolerated, with the safety profile you've come to expect from cephalosporins.[10]

Cost per day,§ CEFOTAN vs cefoxitin

Treatment
Prophylaxis
CEFOTAN
Cefoxitin

In intra-abdominal and gynecologic infection due to indicated organisms

Switch to

CEFOTAN® IM/IV
(cefotetan disodium)

The cost-effective replacement for cefoxitin.

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1. Journal Advertisement, *N Engl J Med*, 1987.

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They said.[2-9]

for treatment in obstetrics and gynecology

"Twice-daily administration of cefotetan is a highly effective single agent for the treatment of mixed aerobic-anaerobic infections in obstetric and gynecologic patients."[2]

2. Sweet RL, Gall SA, Gibbs RS, et al: Multicenter clinical trial comparing cefotetan versus moxalactam or cefoxitin as therapy for obstetric and gynecologic infections. *Am J Surg,* submitted for publication.

"Cefotetan plus doxycycline was demonstrated to be an effective and safe regimen for the treatment of acute PID as measured by early clinical response."[3]

3. Sweet RL, Schacter J, Landers DV, et al: Treatment of hospitalized patients with acute pelvic inflammatory disease: Comparison of cefotetan plus doxycycline and cefoxitin plus doxycycline. *Am J Obstet Gynecol,* submitted for publication.

for treatment in intra-abdominal infection

"98% (93/95) of cefotetan patients and 95% (41/43) of cefoxitin patients had complete resolution or improvement of their signs and symptoms of intraabdominal infection."[4]

4. Wilson SE for the Multicenter Study Group: Cephalosporin therapy in intraabdominal infections: A multicenter randomized comparative study of cefotetan, moxalactam and cefoxitin. *Am J Surg,* submitted for publication.

for prophylaxis in obstetric and gynecologic surgery

"In this evaluation, cefotetan administered in a single dose of 1 gm was more effective as a prophylactic agent than multiple, 2-gm doses of cefoxitin in reducing infectious morbidity in...cesarean section patients."[5]

5. McGregor JA, Gordon SF, Krotec J, et al: Results of a randomized, multicenter, comparative trial of a single dose of cefotetan versus multiple doses of cefoxitin as prophylaxis in cesarean section. *Am J Obstet Gynecol,* submitted for publication.

"Uterine tissue concentration was...well above the minimum inhibitory concentrations required for most gram-positive anaerobes as well as Bacteroides fragilis."[6]

6. Berkeley AS, Freedman KS, Ledger WJ, et al: Comparison of cefotetan and cefoxitin for abdominal and vaginal hysterectomy. *Am J Obstet Gynecol,* submitted for publication.

for prophylaxis in general surgery

"Cefotetan administered as a single 2-gm preoperative dose was as safe and effective as multiple doses of cefoxitin."[7]

7. Jagelman DG, Fabian TC, Nichols RL, et al: Single-dose cefotetan vs. multiple-dose cefoxitin as prophylaxis in colorectal surgery. *Am J Surg,* submitted for publication.

as a cost-effective replacement for cefoxitin

*"Cefotetan therapy cost less than cefoxitin therapy for all types of infections."**[8]

8. Sochalski A, Sullman S, Andriole VT: Cost effectiveness study of cefotetan versus cefoxitin and cefotetan versus combination antibiotic regimens. *Am J Surg,* submitted for publication.

"Cefotetan can provide significant cost savings with neither a compromise in therapeutic effectiveness nor an increased risk of toxicity."[9]

9. Hemsell DL, Wendel GD, Gall SA, et al: Multicenter comparison of cefotetan and cefoxitin in the treatment of obstetric and gynecologic infections. *Am J Obstet Gynecol,* submitted for publication.

*CEFOTAN is indicated for the treatment of intra-abdominal and gynecologic infections due to susceptible pathogens including *Bacteroides* species such as *B fragilis, B bivius,* and *B disiens,* but not *B distasonis, B ovatus,* or *B thetaiotaomicron.*

We all agree.

CEFOTAN® IM/IV
(cefotetan disodium)

Does so much for so much less than cefoxitin

Please see next page for brief summary of prescribing information.

In intra-abdominal and gynecologic infection due to indicated organisms

CEFOTAN® IM/IV
(cefotetan disodium)

Does so much for so much less than cefoxitin

For Intravenous or Intramuscular Use
BRIEF SUMMARY

INDICATIONS AND USAGE

TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary tract infections caused by *E coli, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris, Providencia rettgeri,* and *Morganella morganii*).

Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.

Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis,* Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.

Gynecologic infections caused by *Staphylococcus aureus*† (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis,* Streptococcus* species (excluding enterococci), *E coli, Proteus mirabilis, Neisseria gonorrhoeae, Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*), *Fusobacterium* species,† and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species†).

Intra-abdominal infections caused by *E coli, Klebsiella* species (including *K pneumoniae*†), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*).

Bone and joint infections caused by *Staphylococcus aureus.*†

***NOTE:** Some strains of *Staphylococcus epidermidis* are resistant to cefotetan.

† Efficacy for this organism in this organ system was studied in fewer than ten infections.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile.* Other causes should also be considered.

PRECAUTIONS

GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state. Prothrombin times should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels of Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approx 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approx 2-4 times the usual human dose), only 1 of 10 treated animals was affected, and the degree of degeneration was mild. Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

CEFOTAN® (cefotetan disodium)

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In clinical studies the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5 percent of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4 percent of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2 percent of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2 percent of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than one percent of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

DOSAGE AND ADMINISTRATION

TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dose*	Every 12 hours
10-30	Usual Recommended Dose*	Every 24 hours
<10	Usual Recommended Dose*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED

CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21)

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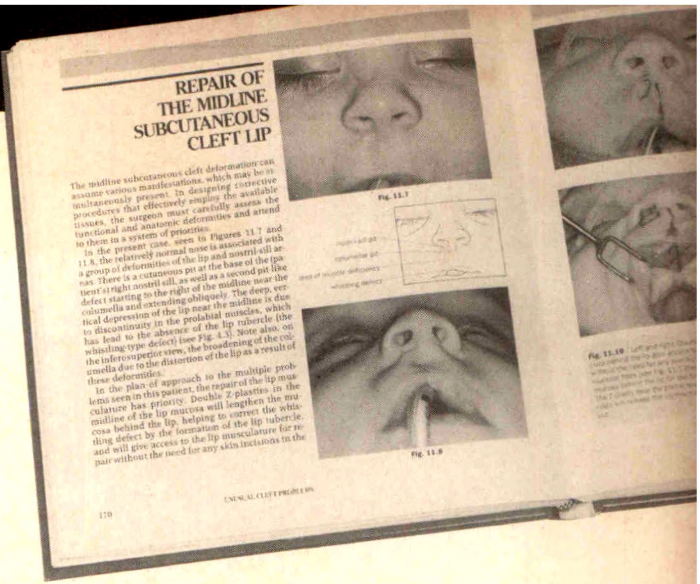

REPAIR OF THE MIDLINE SUBCUTANEOUS CLEFT LIP

The midline subcutaneous cleft deformation can assume various manifestations, which may be simultaneously present. In designing corrective procedures that effectively employ the available tissues, the surgeon must carefully assess the functional and anatomic deformities and attend to them in a system of priorities.

In the present case, seen in Figures 11.7 and 11.8, the relatively normal nose is associated with a group of deformities of the lip and nostril-sill areas. There is a cutaneous pit at the base of the patient's right nostril sill, as well as a second pit-like defect starting to the right of the midline near the columella and extending obliquely. The deep, vertical depression of the lip near the midline is due to discontinuity in the prolabial muscles, which has lead to the absence of the lip tubercle (the whistling-type defect) (see Fig. 4.3). Note also, on the inferosuperior view, the broadening of the columella due to the distortion of the lip as a result of these deformities.

In the plan of approach to the multiple problems seen in this patient, the repair of the lip musculature has priority. Double Z-plasties in the midline of the lip mucosa will lengthen the mucosa behind the lip, helping to correct the whistling defect by the formation of the lip tubercle, and will give access to the lip musculature for repair without the need for any skin incisions in the

170 UNUSUAL CLEFT PROBLEMS

Techniques in CLEFT LIP, NOSE AND PALATE RECONSTRUCTION

...show you the art of reconstructive plastic surgery for children born with cleft deformities

By Donald I. Kapetansky, M.D.

Foreword by D. Ralph Millard, Jr., M.D.

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. . . show you some of the most effective and efficient procedures in use today to correct cleft deformities in children. Sequential photographs of operations show each step of repair. Clear, close-up photographs show cleft deformities from various angles to help you fully understand the patient's condition. Detailed line drawings, full-color schematic diagrams, and explanatory text accompany the photographs and clarify important aspects of the deformities and the surgical techniques employed to correct them.

Complete coverage of surgical procedures

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With 25 years of practice and more than 2500 cleft operations to his credit, the author brings a wide range of experience and an authoritative viewpoint to this work. From a concentration on techniques that require fewer staged procedures, to methods of suturing the skin, to the use of long-acting local anesthetics even with general anesthesia—you'll find a multitude of suggestions for pre- and postoperative care and interoperative planning that aim to ease the strain on children enduring multiple surgical procedures.

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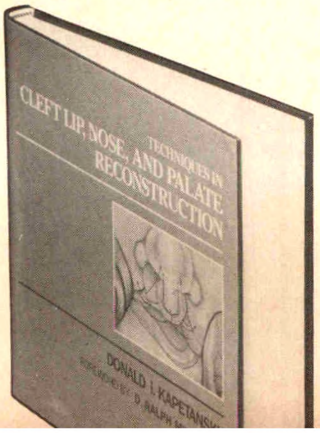

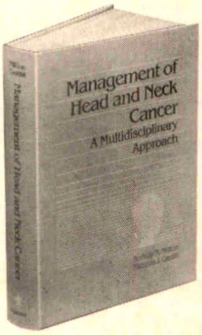

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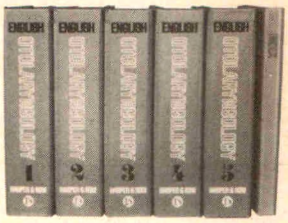

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Liver Transplantation for Malignant Disease

Results in 93 Consecutive Patients

JOHN G. O'GRADY,* REX J. POLSON,* KEITH ROLLES,† ROY Y. CALNE,† and ROGER WILLIAMS*

Ninety-three patients with malignant disease underwent orthotopic liver transplantation between May 1968 and April 1987 in the Cambridge/King's College Hospital program. Of 50 patients with primary hepatocellular carcinoma (HCC) (19 with cirrhosis, 31 without cirrhosis, including 7 with fibrolamellar variant), 37 (74%) survived for more than 3 months, and in this group evidence of tumor recurrence was obtained in 24 (64.9%), the longest survivor being 11.8 years post-transplant, and three survived for more than 5 years. Although there is no correlation between the frequency of tumor recurrence and underlying cirrhosis, or histologic type (except fibrolamellar variant), it was observed earlier in those with moderate/poorly differentiated tumors and also when prednisolone and azathioprine was used for immunosuppression. Tumor recurred in all but two of those with peripheral or central cholangiocarcinoma (one alive at 6.1 years) with median survival times of 34 weeks and 56 weeks for the central and peripheral types, respectively. Among the unusual primary tumors, one with epithelioid haemangioendothelioma developed tumor recurrence at 2 years, one of two patients with apudoma is tumor-free at 2.2 years, and the one patient with bile-duct papillary cystadenocarcinoma is alive at 1.7 years. For the secondary hepatic malignancy group, survival times were shorter with little palliation except for two patients with carcinoid syndrome who were free of associated symptoms at 6 and 10 months. Despite the overall high frequency of tumor recurrence in most categories of hepatic malignancy, liver transplantation gave worthwhile survival with a number of patients cured and in the others considerable palliation of symptoms.

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IN THE EARLY DAYS of clinical liver transplantation, primary malignant disease was a favored indication with less difficult surgery and fewer postoperative complications than when transplantation was carried out for advanced cirrhosis. Up until 1979, over 50% of the transplants performed in the Cambridge/King's College Hospital program were for malignant conditions, although it soon became clear that tumor recurrence was all too frequent. Indeed Starzl has written that this form of treatment is conceptually unsound, this view being based on his results in 54 patients with malignant disease transplanted between 1963 and 1985.[1,2] The only patients in that series without frequent early recurrence were those with small hepatomas found incidentally at transplantation carried out for chronic liver disease and the subgroup of patients with the fibrolamellar variant of hepatocellular carcinoma (HCC).[1,2] Although this view has gained some acceptance, other centers including our own and that of Pichlmayr's at Hannover, have continued to transplant patients with malignant disease on the basis that at least in some instances cure is obtained and in others worthwhile palliation.

For the present report we have analyzed the results obtained in a series of 93 consecutive patients with either primary or secondary malignant liver disease treated by transplantation between May 1968, the beginning of the Cambridge/King's College Hospital program, and April 1987.

Materials and Methods

The 93 patients comprised 50 with primary HCC, 26 with either peripheral or central cholangiocarcinoma, nine with unusual primary tumors (five with angiosarcoma or sarcoma, one with epithelioid haemangioendothelioma, two with apudoma, and one with bile-duct papillary cystadenocarcinoma), and 8 with secondary hepatic malignancy including two with the carcinoid syndrome. Of the 50 patients with HCC, 19 had an underlying cirrhosis. The 31 cases arising in a noncirrhotic liver included seven with the fibrolamellar variant (Table 1). There were five patients in the cirrhotic group and three noncirrhotic cases with evidence of hepatitis B virus infection; these included one patient without cirrhosis in whom the only marker was HBV-DNA integration in tumor cells. Four of the patients in the non-

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TABLE 1. *Data Relating to Groups of Patients Treated with Primary Hepatic Malignancy*

Malignancy	N	Age (yr) Median	Age (yr) Range	Sex Distribution (M:F)	Interval Between Onset of Symptoms and Transplant
Hepatocellular carcinoma					
Cirrhotic	19	50	5–59	15:4	6 mo (3 wk–6 mo)
Noncirrhotic	24	42	10–61	10:14	6 mo (3 wk–9 mo)
Fibrolamellar	7	23	14–51	1:6	5 mo (3–12 mo)
Central cholangiocarcinoma	13	46	16–53	7:6	8 mo (2–24 mo)
Peripheral cholangiocarcinoma	13	49	28–64	7:6	6 mo (4 wk–18 mo)
Bile-duct papillary cystadenocarcinoma	1	36		1:0	2 mo
Primary sarcoma/angiosarcoma	5	32	4–49	2:3	6 mo (3–10 mo)
Epithelioid hemangioendothelioma	1	30		0:1	8 mo
Apudoma	2	34, 36		1:1	2, 4 yr

cirrhotic group had a history of long continued oral contraceptive pill usage.

Six of the cirrhotic patients with HCC had solitary tumors ranging from 2.7 to 6 cm, and 13 had multifocal tumors between 5 and 10 cm in diameter. Tumor masses were generally larger in the noncirrhotic group, and 19 of the 31 cases had a single large lesion of 8–21 cm in diameter, with associated smaller satellite lesions in seven instances. In 12 cases there were multiple masses of between 8 and 15 cm in diameter. Tumor masses in peripheral cholangiocarcinomas were of similar size (8–19 cm in diameter with several discrete masses in six cases); the central cholangiocarcinoma tumors (presenting as biliary obstruction) comprised mainly small scirrhous lesions. Seven of these had been previously treated by surgical insertion of a stent. Two of the cases had a long history of sclerosing cholangitis.

The two patients with apparently primary hepatic apudomas were first diagnosed 2 and 4 years previously and had large tumor masses with increased circulating levels of glucagon/somatostatin and calcitonin/gastrin/pancreatic polypeptide, respectively. The secondary hepatic deposits group included two patients with the carcinoid syndrome and large multiple masses throughout the liver whose symptoms (diarrhea, flushing) were disabling and no longer responded to pharmacologic therapy and repeated hepatic artery embolization. Four patients had earlier resections of a primary tumor elsewhere and in the remaining two cases the extrahepatic primary was removed at the time of transplantation (Table 2).

TABLE 2. *Data Relating to the 8 Patients with Secondary Hepatic Malignancy Treated by Transplantation*

Primary Tumor	Age (yr)	Sex	Resection of Primary
Meningiosarcoma	31	F	4 years previously
Colon	31	F	3 mo previously
Pancreas (tail)	45	F	3 mo previously
Nephroma	54	M	At transplantation
Leiomyosarcoma	57	M	At transplantation
Colon	45	M	11 mo previously
Carcinoid of small bowel	48	M	2 yr previously
Carcinoid of lung	51	F	4 yr previously

In screening for extrahepatic spread, ultrasonographic examination of the upper abdomen, CT scan of thorax and abdomen (replacing whole lung tomography and abdominal lymphangiography used in the earlier patients), and radioisotope bone scanning were carried out routinely. Radiologically demonstrable tumor invasion of a resectable portion of the portal vein was not considered an absolute contraindication to transplantation. In addition, six patients had an exploratory *mini-laparotomy* as part of the transplant workup.

The transplant operation was carried out as described elsewhere.[3] Biliary reconstruction was obtained using predominantly choledochocholedochostomy up to 1975 and thereafter with the biliary conduit technique, except in patients with primary sclerosing cholangitis who had a Roux-en-Y anastomosis.

Sixty-six of the 93 patients had had a previous surgical procedure related to the malignancy (Table 3) including the six patients who had a mini-laparotomy as part of transplantation workup already referred to. In five of these patients a hepatic resection was attempted but not found to be feasible. One of the six patients with previous successful local resection underwent enucleation of a 4-cm HCC from a cirrhotic liver in Japan 2 years prior to transplantation, and there were four cases in the noncirrhotic HCC group who had resections 8 months, 2 years, 3.5 years, and 5.5 years previously, while the final patient had five previous resections spanning a 10-year period.

Statistics

Statistical methods employed include Kaplan-Meier cumulative survival curves, chi square test with Yates correction, and the Mann-Whitney U test.

Results

Primary Hepatocellular Carcinoma

Three-month survival figures were 68.5% for those with an underlying cirrhosis and 77.4% for the noncir-

TABLE 3. *Surgical Procedures Prior to Liver Transplantation*

Diagnosis	No. of Cases	Mini-laparotomy (%)	Exploratory Laparotomy (%)	Attempted Resection (%)	Previous Resection (%)
HCC with cirrhosis	19	2 (10.5)	5 (26.3)	—	—
HCC without cirrhosis	31	3 (9.7)	11 (35.5)	4 (12.9)	5 (16.1)
Central cholangiocarcinoma	13	—	12 (92.3)	—	—
Peripheral cholangiocarcinoma	13	8 (61.5)	1 (7.7)	1 (7.7)	—
Sarcoma/angiosarcoma	5	3 (60)	—	—	—
Other primary tumours	2	1 (50)	—	—	—
Apudoma	2	2 (100)	—	—	—

rhotic group (Fig. 1). Deaths during this early period were due to operative and postoperative hemorrhage (42%), graft failure (25%), sepsis (25%), and chronic rejection (8%). Patients in the noncirrhotic group who had undergone a previous resection or exploratory laparotomy (including mini-laparotomy) had a higher mortality rate (5/20 *vs.* 0/11, $p < 0.05$). There was a similar trend in the cirrhotic patients, but it did not reach statistical significance (3/6 *vs.* 3/13, $p > 0.05$).

After 3 months, the survival curves for the cirrhotic and noncirrhotic groups were also similar with 1- and 2-year survival rates, respectively, of 42.5% and 37.3% as compared to 48.5% and 38.3% (Fig. 1). Tumor recurrence accounted for 59% of the deaths after 3 months, while the remainder were due to sepsis (22.7%) and chronic rejection (9.1%) with single instances of mitozanthrone cardiotoxicity and carotid artery erosion complicating prolonged endotracheal intubation for chronic respiratory failure. Twelve of these patients survived for more than 1 year including two who were free of tumor at the time of death over 5 years post-transplantation. Of the ten patients in this series who are currently alive (as of October 1, 1987), there are five who are more than 1 year post-transplantation, with two of these alive at 4.8 and 11.8 years and free of detectable tumor.

Tumor Recurrence

Tumor recurrence was diagnosed in 24 (64.9%) of 37 patients who survived at least 3 months post-transplantation with no difference between the cirrhotic (69.2%) and noncirrhotic groups (60.0%). Eleven patients were asymptomatic with respect to tumor recurrence at the time this was detected and remained so for a further median period of 6 months (range: 2–13 months). Evidence of recurrence was based on an increase in serum alpha-fetoprotein level (0.7–1.7 years post-transplantation) or appearance of metastases on chest X-ray, ultrasonographic examination, or CT scan (at 3 weeks to 3.3 years) (Fig. 2). The most common clinical signs comprised return of original symptoms (abdominal discomfort, nausea and vomiting, weight loss), pyrexia, skin/buccal mucosa nodules, and pain from skeletal deposits. The principal sites of documented tumor recurrence in the 23 patients were liver (57.9%), lung (57.9%), adrenal (42.1%), bone (26.3%), abdominal cavity (21.1%), and skin (15.8%). In two of four patients with skin metas-

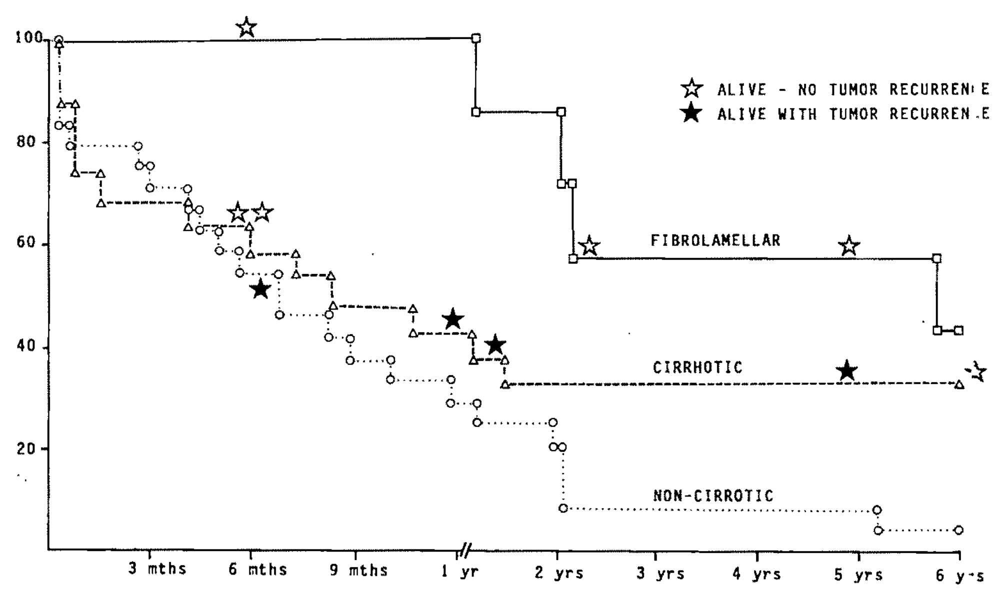

FIG. 1. Kaplan-Meier survival curves for patients transplanted with fibrolamellar HCC and nonfibrolamellar HCC arising in cirrhotic and noncirrhotic livers.

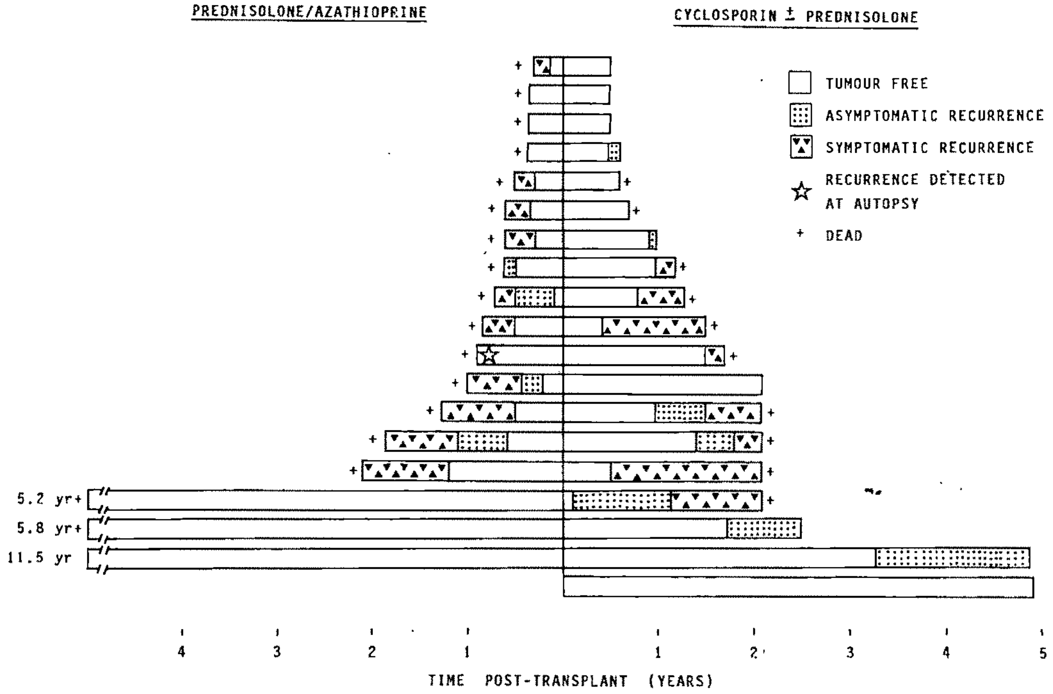

FIG. 2. Overall survival in patients transplanted for HCC and immunosuppressed with prednisolone/azathioprine (1967–1979) or cyclosporine and prednisolone (1980–1987) with breakdown for oncologic-free periods and duration of asymptomatic and symptomatic tumor recurrence.

tases, isolated lesions developed at the site of puncture for a liver biopsy or percutaneous cholangiogram performed prior to transplantation. Ten of the patients who developed recurrence were totally free of symptoms for more than 1 year including one remarkable patient who remains well at 4.8 years with tumor regression on chemotherapy using mitozanthrone and 5-fluorouracil.

Among the seven patients with the fibrolamellar variant of HCC, tumor recurrence was detected in three patients at 6, 9, and 18 months, leading to death at 1.1–2.2 years. Three patients are alive and free of detectable tumor at 3-months, 1.8 years, and 4.5 years, respectively, while the remaining patient was free of tumor when she died 5.8 years post-transplant from sepsis and variceal bleeding complicating the development of cirrhosis (from a transfusion acquired non-A, non-B hepatitis).

The median interval between transplantation and death from recurrence was longer in patients with a well-differentiated tumor on histologic examination than in those with a moderate/poorly differentiated tumor (2 years and 33 weeks, respectively; $p < 0.05$) and all three patients free of detectable malignancy at 2 years had well-differentiated tumors. No correlation was found between tumor size and frequency or rapidity of recurrence, although it is noteworthy that one patient with a 21-cm tumor with multiple smaller lesions was free of tumor at 5.2 years post-transplantation. No correlation was found between tumor recurrence and previous surgery in the noncirrhotic patients surviving more than 3 months (54.5% and 60.0%, respectively), although in the cirrhotic group all three patients who had a previous laparotomy (two exploratory, one minilaparotomy) developed recurrence as compared to four of ten patients who had not had previous surgery.

Comparison of tumor recurrence rates for the two main immunosuppression regimens used in the program showed no difference between 18 patients maintained on prednisolone/azathioprine and 19 on cyclosporin ± prednisolone (66.7% and 63.2%, respectively), although median survival was longer in the cyclosporin-treated group (9 months and 15 months, respectively; $p < 0.05$). The interval between the time of transplantation and detection of tumor recurrence was also greater in patients on cyclosporin (median: 12 months; range: 3 weeks to 3.3 years) than in the prednisolone/azathioprine group (median: 6 months; range: 4 weeks to 1.2 years; $p < 0.05$). Since nine of the patients on cyclosporin (47.4%) are currently alive as compared to only one in the prednisolone/azathioprine group, it is likely that this difference will become even further accentuated.

Changes in Alpha-fetoprotein

Serial levels for six of the earlier patients have previously been published,[4] indicating a return to within the normal range (<10 ng/mL) in four cases with a half-life of 3–8.5 days. One of these patients continues to have a normal level at 11.8 years, but in the other three patients within 4 months of transplantation the levels had increased again to above the normal range. Since then there have been a further six cases in whom serum alpha-fetoprotein levels have returned to normal following the transplant. Two of these remain negative at 4–8 months (Fig. 3), and in two patients the level remained in the normal range for at least 10 months before rising again in association with recurrent disease. The sixth patient had only a modest rise in alpha-fetoprotein (31 ng/mL) at 1 year when tumor recurrence was diagnosed.

Cholangiocarcinoma and Other Primary Tumors

Survival curves for both the central and peripheral cholangiocarcinomas are similar (Fig. 4) with 3-month survival rates for both of 53.8%. Sepsis was the major cause of death during this period (81.8%), with hemorrhage (9.1%) and acute graft failure (9.1%) much less frequent. One-year survival rates were also similar for the central and peripheral tumors (30.7% and 38.4%, respectively).

Of the seven patients with central cholangiocarcinoma who survived 3 months, six have documented recurrence of tumor (abdomen five, lung four, bone two, liver one, and skin at operative drain site one) leading to death, a median of 34 weeks post-transplantation. One patient without tumor recurrence who had presented with obstructive jaundice due to a 13-cm cholangiocarcinoma at the hilum is alive and well at 6.5 years. One of the seven patients with peripheral cholangiocarcinoma died at 4 months as a consequence of an intracerebral vascular accident. The other six developed recurrence of tumor (abdomen five, lungs three, liver two, bone two, and cervical lymph nodes one), but the median survival for this subgroup was longer at 1.1 years (range: up to 3.2 years) compared with the central cholangiocarcinoma patients.

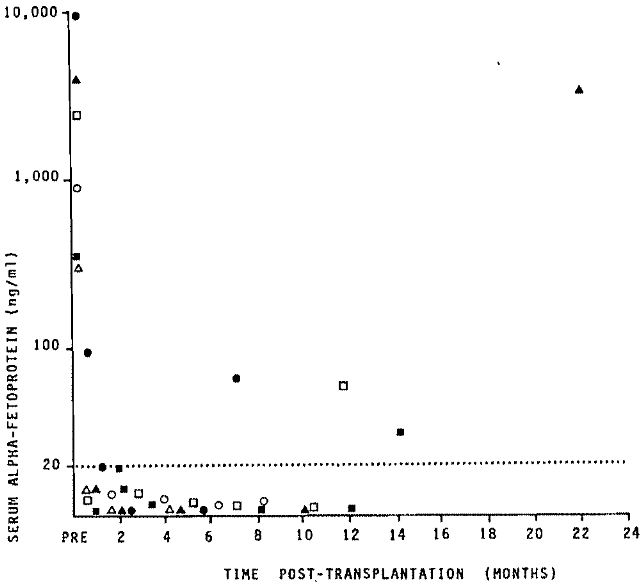

FIG. 3. Serial alpha-fetoprotein levels in six patients with elevated levels pretransplant, which returned to the normal range after surgery.

Four of five patients with primary sarcoma/angiosarcoma died within 7 weeks of surgery as a consequence of hemorrhage or sepsis and the remaining patient has tumor recurrence at 6 months. The single case of epithelioid hemangioendothelioma was in good health for 22 months but then developed rapidly progressive hepatomegaly in association with an apparent microangiopathic hemolytic anemia and impaired renal function, leading to death 2 months later. At autopsy the liver graft was extensively replaced by tumor with no evidence of malignancy elsewhere. The single patient with bile-duct papillary cystadenocarcinoma is alive and free of detectable tumor 20 months after transplantation as

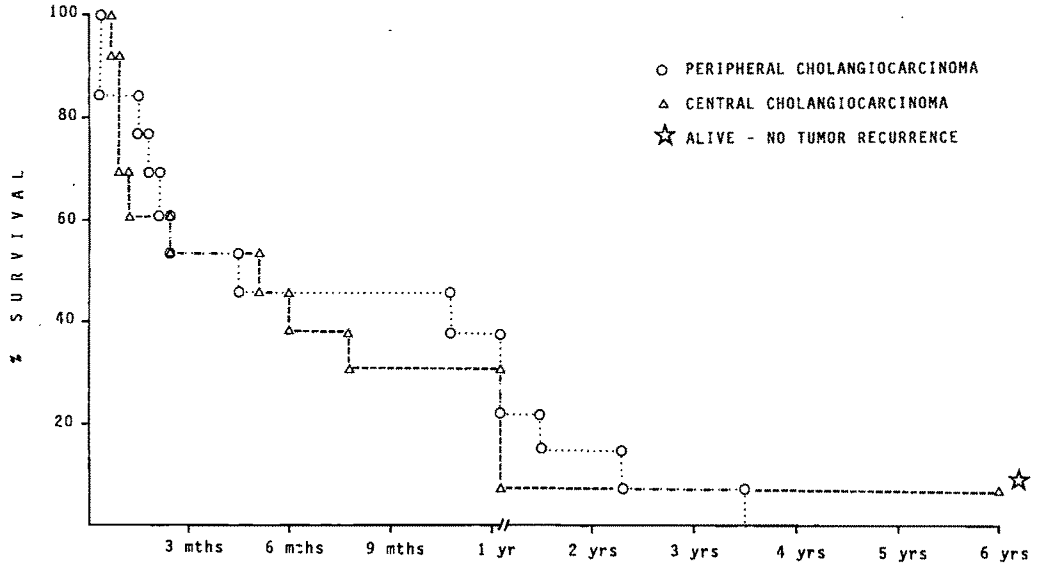

FIG. 4. Kaplan-Meier survival curves for patients transplanted with peripheral and central cholangiocarcinoma.

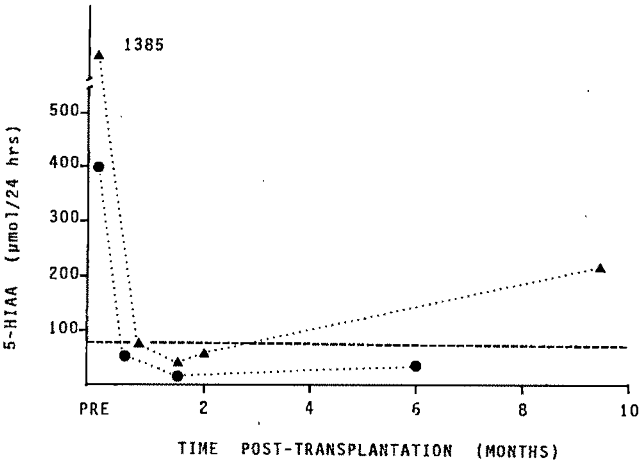

FIG. 5. Urinary excretion of 5-HIAA preliver and postliver transplantation for the carcinoid syndrome.

is one of the two patients with apudomas (2.2 years after transplantation). The other patient with an apudoma had no evidence of recurrence at the time of death from chronic graft rejection (7 months).

Secondary Hepatic Malignancy

Only three of the six patients transplanted for hepatic metastases survived for 3 months, and these died between 22 and 41 weeks from recurrent disease. Of the two patients with the carcinoid syndrome, one died at 7 months with chronic rejection with a normal 5-HIAA excretion; the other is symptom-free at 12 months with no radiologic evidence of tumor recurrence but with increasing levels of 5-HIAA excretion, initially detected at 9.5 months (Fig. 5).

Discussion

The high recurrence rates of primary HCC following transplantation, even in the most recent cases, can only be considered disappointing. Although there have been a number of advances in radiologic techniques for the detection of extrahepatic spread prior to surgery, these are still subject to considerable limitations. Thus, in one recent study of CT scanning, 20–47% of various patient groups had macroscopic tumor nodules at the time of surgery that were not apparent on scanning.[5] It seems reasonable to assume that recurrence of tumor following transplantation is based on microdeposits already present in extrahepatic sites or released during surgical manipulation. Of particular interest was the finding that in cases with a raised alpha-fetoprotein level in serum postoperatively, this could fall to and remain within a normal range for periods of up to 10 months before rising again in association with other evidence of tumor recurrence. Whether adjuvant chemotherapy after transplantation could prolong this interval further or prevent recurrence from developing remains to be established.

The most favorable results reported are those with small asymptomatic tumors found incidentally at the time of transplantation, with 12 of 13 such patients in the Starzl et al. series remaining free of tumor recurrence between 4 months and 15 years (median: 16 months).[1] Most of the cases in the present series that were detected by screening of cirrhotic patients by ultrasonographic examination and alpha-fetoprotein levels had larger tumors than this (>2.7 cm), indicating the need for even more intensive screening of high-risk groups. The recurrence rate in our series with the larger primary HCC tumors was lower at 64.9% than the 77.8% in Starzl's series.[1] In addition, long-term cures were obtained in patients who had not been suitable for hepatic resection because of the localization or extent of tumor or the presence of cirrhosis, and in the remainder considerable palliation was often achieved particularly with well-differentiated tumors and when cyclosporin was used as the main immunosuppressive agent. In several cases subsequent chemotherapy, and in two instances surgical removal of isolated secondary deposits in the adrenal gland, appeared to prolong the period of worthwhile palliation and survival.

The present experience would, however, be in accord with the data of Starzl et al. with respect to the fibrolamellar variant of HCC as the best subgroup, in which 1-year survival was 100% in both series of seven cases each and with overall recurrence rate of 50%.[2] Good results are also obtained with this tumor when local resection is feasible as demonstrated by the study of Soreide et al. of seven patients who survived for between 8 and 41 months with one instance of tumor recurrence during this period.[6]

Whether tumor growth is accelerated by immunosuppression following transplant is difficult to determine. In the present study it is of interest that the rate of growth appears to be slower in patients maintained on cyclosporin, as suggested by the longer median tumor-free interval (12 months) post-transplantation and the longer lag period before the reappearance of alpha-fetoprotein in serum. In the study by Iwatsuki et al.[1] the median interval between transplantation and HCC was only 4 months, but many of these patients were probably treated in the precyclosporin era. The possible acceleration of tumor growth by immunosuppressive therapy was one of the factors prompting the conclusion of Iwatsuki et al. that transplantation for malignant disease was conceptually unsound.[1] We believe this conclusion needs to be reconsidered with greater dependence on cyclosporin, especially since a median oncologically free interval of 1 year provides a good basis for worthwhile palliation.

The chances of a potentially curative resection of central (bile-duct) cholangiocarcinoma being possible are small, as indicated in the study by Blumgart et al. in which only 18 of 94 patients with hilar cholangiocarcinoma were treated in this way, and these had a mean survival of 17 months.[7] A greater percentage of such patients are amenable to treatment by transplantation, and our 3-month survival rate of 53.8% is similar to the 50% achieved by Iwatsuki et al.[1] However, only two patients in both studies have remained free of tumor. No patient with peripheral cholangiocarcinoma has to date been cured of tumor, although a median survival of 1.1 years with a range of up to 3.5 years represents worthwhile palliation. Poor results with primary angiosarcoma/sarcoma are not surprising, but the recently recognized variant, epithelioid hemangioendothelioma, with a much less aggressive natural history remains a worthwhile category.

Patients with apudomas and secondary carcinoid tumors constitute a special group with respect to liver transplantation. Not only is tumor growth naturally slow with these tumors, but the dramatic relief of associated symptoms obtained with a successful graft, particularly the disabling carcinoid syndrome, is a remarkable event to witness.

Our results do little to support the use of transplantation for patients with secondary hepatic malignancy (excluding carcinoid). Pichlmayr et al., however, considered the palliation conferred by transplantation to be valuable despite the short period of survival.[8] The most encouraging data comes from the Vienna group who reported a 70% 1-year survival in ten patients, with one patient free of detectable tumor at 3 years.[9] There is also a single patient in the UCLA series with metastatic gastric leiomyosarcoma who is alive and free of detectable tumor 21 months post-transplantation.[10] At least some categories of patients within this group probably merit reconsideration with regard to transplantation, especially those with hepatic metastases for a primary colonic carcinoma resected some years previously.

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Surgical Procedures among Those $\geq$90 Years of Age

A Population-based Study in Olmsted County, Minnesota, 1975–1985

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Persons $\geq$ 90 years of age represent a rapidly growing subset of the population, but little data exist on their utilization of the health care system. Population-based data capabilities of the Rochester/Olmsted County Epidemiology Project were used to study the performance of surgery among persons $\geq$ 90 years of age for the 11-year period, 1975–1985. During this time, 224 residents of Olmsted County, Minnesota underwent 301 separate operations. The annual operation rate increased over the course of the study (trend test, $p < 0.001$), reaching a plateau of 89.0 per 1000 person-years. This suggests a potential for nearly 91,000 operations annually in this age group based on 1987 U.S. Census estimates. Ninety-two per cent were discharged from the hospital alive, and 5-year survival was consistent with that expected (23% *vs.* 17%). Increased longevity of the general population, combined with increased performance of surgery in this rapidly growing segment of the population, may have significant implications for health care planning.

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THERE is little information on the utilization of the health care system by people $\geq$ 90 years of age. The federal government, for example, considers all persons $\geq$ 65 years of age a single cohort for data collection and future projections. Attempting to fill this information gap, Torrey[1] found that people > 80 years of age received 77% more Medicare dollars than people 65 to 69 years of age, amounting to about \$50 billion per year. This has somewhat ominous implications economically because the very old represent a rapidly growing segment of the U.S. population. People $\geq$ 90 years of age will number an estimated 1,901,000 by the year 2000.[2] This represents a compound annual growth rate of 4.4%, or a 236% increase between 1980 and the end of the century.[2,3] A further dramatic rise will occur as the baby boom cohort reaches advanced age.

In addition to these dramatic demographic changes, it was our impression that more elderly individuals were undergoing surgical procedures over the past decade. If true, future costs of medical care for this segment of the population may be even greater than currently projected, and additional surgical resources will be required. Consequently, we studied the performance of surgery among residents of Olmsted County, Minnesota, who were $\geq$90 years of age during the 11-year period, 1975–1985.

Methods

It was possible to undertake this study in Olmsted County, Minnesota because the diagnoses made and the surgical procedures performed on County residents by virtually all medical care providers are indexed, and the original medical records can readily be retrieved for review. The value of this data system, the Rochester/Olmsted County Epidemiology Project, for population-based studies has been described previously.[4,5]

During the 11-year period, 1975–1985, 301 operations involving 319 procedures were performed at the Mayo Clinic on 224 Olmsted County residents $\geq$ 90 years at the time of surgery. None of the other county physicians operated on any Olmsted County resident in this age group. Only permanent residents of Olmsted County were included.

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TABLE 1. *Utilization of Surgery Counting Individual Patients, Total Operations, or all Surgical Procedures among Olmsted County, Minnesota Residents ≥90 Years of Age, 1975–1985.*

Total Surgery	Men			Women			Both Sexes		
	N	Rate*	95% CI	N	Rate*	95% CI	N	Rate*	95% CI
Patients	73	91.4	71.6–114.9	151	51.4	43.5–60.2	224	59.9	52.3–68.3
Operations	99	123.9	100.7–150.8	202	68.7	59.6–78.9	301	80.5	71.7–90.1
Procedures	106	132.7	108.6–160.4	213	72.4	63.1–82.9	319	85.3	76.2–95.2

Confidence intervals (CI) are based on Poisson distribution.

* Annual incidence per 1000.

Each patient was classified preoperatively according to the physical status classification (ASA class) of the American Society of Anesthesiologists,[6] and preoperative medical conditions were determined by individual chart review. At our institution, patients are required to undergo a preanesthetic medical examination by an internist prior to a surgical procedure, and, in addition, all patients complete a questionnaire detailing their medical history. Moreover, because Mayo utilizes a unit record system, the complete history containing outpatient as well as inpatient data is available for review. Hypertension, angina, chronic obstructive pulmonary disease, endocrine disease, and arrhythmia were defined as present if the patient was receiving medical therapy for the condition at the time of operation. Previous myocardial infarction was identified by the presence of Q-waves on electrocardiogram. Prior coronary artery bypass or cardiac valvular surgery were recorded. Smoking history was obtained from the patient questionnaire. A preoperative creatinine level > 2.0 mg/dL or the use of dialysis indicated renal dysfunction. Prior malignancy as well as surgery, chemotherapy, or radiation therapy for malignancy were recorded. Central nervous system disease was identified in patients with medically documented cerebral vascular accident, transient ischemic attack, or neurologic deficit of central origin. Biliary disease was present if the total bilirubin was >3.0 mg/dL, alkaline phosphatase > 375 U/L, or AST > 45 U/L.

Per capita utilization rates were calculated as incidence rates (incidence density) per 1000 person–years (p–y), assuming the entire population in this age group

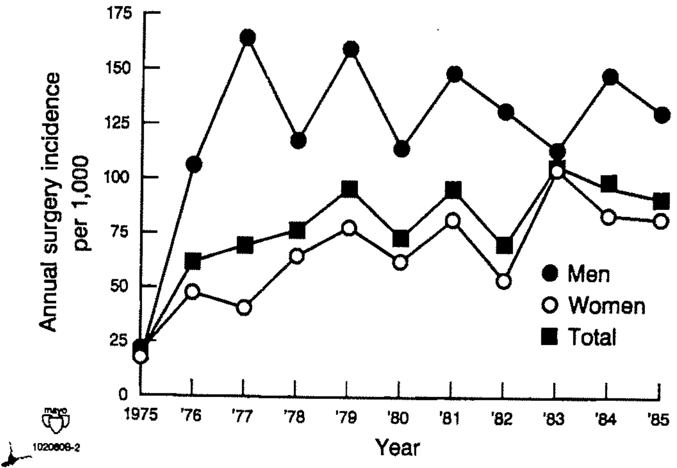

FIG. 1. Utilization of surgery by Olmsted County, Minnesota residents ≥ 90 years of age (1975–1985) by sex and year counting operations.

TABLE 2. *Characteristics of Olmsted County, Minnesota Residents ≥90 Years of Age Undergoing Surgery, 1975–1985*

Patient Characteristic	Operations	
	N*	%*
Being treated for hypertension	131	43.5
Arrhythmia	94	31.2
Previous CNS disease (CVA, TIA, or deficits)	81	26.9†
Prior myocardial infarction (ECG criteria)	75	24.9†
Previous cancer	74	24.6
Being treated for angina	57	18.9
Previous endocrine disease (diabetes or thyroid)	37	12.3
Previous biliary disease (total bilirubin > 3.0 mg/dL or AST > 45 U/L or alkaline phosphatase > 375 U/L)	20	6.6†
Previous renal disease (dialysis, creatinine > 2.0 mg/dL)	16	5.3†
Being treated for COPD	6	2.0
Cigarette smoking status		
Never smoked	192	63.8
Past (stopped >2 months ago)	47	15.6
Current smoker	14	4.6
Unknown	48	16.0
ASA status		
1	0	0.0
2	46	15.3
3	193	64.1
4	58	19.3
5	4	1.3

Individuals may be counted more than once.

* N refers to the number of operations in surgical patients ≥90 years of age for which the patient had the condition(s) listed. The percent uses as a denominator for all characteristics 301, the total number of operations performed.

† Previous CNS disease status is unknown in four patients; prior myocardial infarction status is unknown in two patients; previous biliary status is unknown in 56 patients; previous renal disease status is unknown in nine patients.

TABLE 3. *Distribution of Indications for Surgical Procedure among Olmsted County, Minnesota Residents ≥90 Years of Age Undergoing Surgery 1975–1985*

Indication	ICD-9-CM Codes*	Men		Women		Deaths ≤48 Hours‡		Deaths ≤30 Days‡	
		N	%†	N	%†	N	%	N	%
Disease of musculoskeletal system/ connective tissue	710-739	2	1.9	4	1.9	0	0.0	0	0.0
Fracture of femur	820-821	18	17.0	52	24.4	2	2.9	6	8.6
Other fracture	800-819, 822-829	1	0.9	9	4.2	0	0.0	0	0.0
Disease of digestive system	520-579	26	24.5	43	20.2	4	5.8	10	14.5
Disease of nervous system/sense organs	320-389	3	2.8	36	16.9	0	0.0	0	0.0
Disease of circulatory system	390-459	10	9.4	9	4.2	1	5.3	2	10.5
Disease of genitourinary system	580-629	14	13.2	3	1.4	0	0.0	0	0.0
Disease of skin/subcutaneous tissue	680-709	1	0.9	6	2.8	0	0.0	0	0.0
Disease of respiratory system	460-519	2	1.9	2	0.9	0	0.0	1	25.0
Malignant neoplasm	140-208	16	15.1	21	9.9	3	8.1	7	18.9
Benign neoplasm	210-229	4	3.8	5	2.4	0	0.0	0	0.0
Other neoplasms	230-239	0	0.0	1	0.5	0	0.0	0	0.0
Systems/signs/ill-defined conditions	780-799	7	6.6	21	9.9	1	3.6	2	7.1
Miscellaneous	—	2	1.9	1	0.5	0	0.0	0	0.0
Total (denominator for percentages listed above)	—	106	—	213	—	—	—	—	—

* Data from The International Classification of Diseases, 9th Revision, Clinical Modification, Vol. 1. Ann Arbor, MI: Edwards Brothers, 1987.

† Percentage of all indications.

‡ Deaths in ≤48 hours include intraoperative. Deaths in ≤30 days include intraoperative, hospital in ≤30 days and post-hospital in ≤30 days. Percentages use as a denominator the number of men and women having that indication.

to be at risk. Since Olmsted County data are available only for the age group ≥ 85 years, the Olmsted County population ≥ 90 years of age at the 1980 census was estimated using the 1980 census population for age ≥ 85 years for Olmsted County multiplied by the proportion of these who were ≥90 years old in 1980 census data for Minnesota. For individual calendar years 1975–1979, the 1980 numbers were decreased by the compound annual growth rate for each sex based on the U.S. white population age ≥ 90 years in the 1970 and 1980 census reports.[3,7] For years 1981–1985, the 1980 numbers were increased according to U.S. white population projections.[2,8] Summing these over the 11-year period produced a denominator for the surgery utilization rates of 3,739 p-y (799 p-y in men, 2940 p-y in women). Survival curves were estimated using Kaplan-Meier methodology.[9] Expected survival curves for deaths from all causes were computed for persons of like age, sex, and calendar year of birth, based on cohort life tables constructed for the West North Central region of the United States.[10]

Results

In the 11-year period, 1975–1985, 224 Olmsted County, Minnesota, residents who at the time of surgery were ≥90 years of age underwent 301 separate operations at which 319 specific surgical procedures were performed. Among residents having surgery, most (163, 73%) had only one operation during this interval, but 48 (21%) had two and 13 (6%) had three or more. Of the total operations in this group, two-thirds were in women, but the incidence of operations was over 80% greater in men. A similar excess among males was seen whether surgical utilization was based on individual patients, on total operations, or on all surgical procedures (Table 1).

The overall annual operation rate among Olmsted County residents ≥ 90 years of age was 80.5 per 1000 (95% confidence interval: 71.7–90.1). However, the number of operations rose from five per year in 1975 to 40 per year in 1985. Even with these limited numbers of cases, an increase in the operation rate was apparent over the course of the study (trend test, $p < 0.001$), with the appearance of a plateau for the final 8 years (Fig. 1). This suggests for 1987 a potential for 90,958 operations annually in this age group if the average annual rate over the last 8 years of 89.0 per 1000 were applied to the total U.S. estimated population for 1987 of 1,022,000 individuals ≥ 90 years of age.

Of the total 301 operations, 23% were in individuals

TABLE 4. *Distribution of Surgical Procedures among Olmsted County, Minnesota Residents ≥90 Years of Age Undergoing Surgery 1975–1985*

	Men		Women		Deaths ≤48 Hours†		Deaths ≤30 Days†	
Procedure	N	%*	N	%*	N	%	N	%
Operations on musculoskeletal system	27	25.5	70	32.9	2	2.1	6	6.2
Amputations	6	5.7	1	0.5	0	0.0	0	0.0
Hip and pelvis, including fractures	17	16.0	56	26.3	2	2.7	6	8.2
Reduction of long bone fractures	1	0.9	2	0.9	0	0.0	0	0.0
Others	3	2.8	11	5.2	0	0.0	0	0.0
Operations on digestive system	33	31.1	52	24.4	7	8.2	18	21.2
Laparotomy	3	2.8	5	2.3	4	50.0	5	62.5
Esophagus and stomach procedures	6	5.7	5	2.3	1	9.1	2	18.2
Biliary and liver procedures	5	4.7	10	4.7	1	6.7	4	26.7
Bowel, rectal, anal procedures	9	8.5	17	8.0	1	3.8	5	23.8
Herniorrhaphy	9	8.5	2	0.9	0	0.0	1	9.1
Others	1	0.9	13	6.1	0	0.0	1	7.1
Operations on eye	3	2.8	35	16.4	0	0.0	0	0.0
Operations on cardiovascular system	9	8.5	24	11.3	1	3.0	1	3.0
Major artery procedures, including aortic aneurysm	3	2.8	2	0.9	1	20.0	1	20.0
Peripheral artery procedures, including embolectomy	1	0.9	2	0.9	0	0.0	0	0.0
Pacemaker insertion	5	4.7	19	8.9	0	0.0	0	0.0
Others	0	0.0	1	0.5	0	0.0	0	0.0
Operations on genitals	12	11.3	7	3.3	0	0.0	0	0.0
Prostate procedures	11	10.4	—	—	0	0.0	0	0.0
Others	1	0.9	7	3.3	0	0.0	0	0.0
Operations on skin	5	4.7	12	5.6	0	0.0	0	0.0
Excision of lesions and tumors	1	0.9	8	3.8	0	0.0	0	0.0
Breast biopsy and mastectomy	0	0.0	2	0.9	0	0.0	0	0.0
Others	4	3.8	2	0.9	0	0.0	0	0.0
Operations on urinary system	6	5.7	2	0.9	0	0.0	0	0.0
Operations on respiratory system	5	4.7	3	1.4	1	12.5	3	37.5
Operations on nervous system	3	2.8	2	0.9	0	0.0	0	0.0
Operations on ear, nose, mouth, and throat	1	0.9	2	0.9	0	0.0	0	0.0
Operations on hemic and lymphatic system	1	0.9	0	0.0	0	0.0	0	0.0
Operations on endocrine system	0	0.0	0	0.0	—	—	—	—
Miscellaneous procedures	1	0.9	4	1.9	0	0.0	0	0.0
Angiography	1	0.9	2	0.9	0	0.0	0	0.0
Others	0	0.0	2	0.9	0	0.0	0	0.0
Total (denominator for percentages listed above)	106	—	213	—	—	—	—	—

* Percentage of all procedures.

† Deaths in ≤48 hours include intraoperative. Deaths in ≤30 days include intraoperative, hospital in ≤30 days and post-hospital in ≤30 days. Percentages use as a denominator the number of men and women having procedure.

95 years of age and older, while 2.3% were 100 years of age or more. Not surprisingly, a substantial proportion of these elderly individuals had one or more chronic diseases or conditions (Table 2). These data are reliable despite any cognitive difficulties in the patients because their documented length of medical care at Mayo prior to surgery averaged 44.3 years (median: 50 years), and this complete record was available for review. The prevalence of preoperative disease is reflected in the ASA status of this group, with 85% ASA Class 3 (severe systemic disturbance or disease) or worse.

The indications for surgery, as classified by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), were distributed into 14 major categories (Table 3). Diseases of the digestive system and fractures of the femur were most common (22.0% each), followed by diseases of the nervous system and sense organs (12.2%). The ICD-9-CM system is a clinical index that allows differentiation among diseases specific to a system and disease processes that may occur in that system. For example, the classification of diseases of the digestive system includes diseases specific to it, such as hernias or peptic ulcers, but does not include neoplasms that may occur in it (or elsewhere). These neoplasms are classified separately.

Nearly half (47%) of the operations involved general

TABLE 5. *Causes of Death*

Time of Death	No. of Patients	No. Dying and Cause of Death*
Intraoperatively	7	3, infarcted bowel 2, carcinomatosis 1, ruptured abdominal aortic aneurysm 1, myocardial infarction during total hip arthroplasty
Within 48 hours of operation (not including intraoperative period)	4	1, infarcted bowel 1, pulmonary embolis following hip pinning 1, carcinomatosis 1, pneumonia and sepsis
Within 30 days of operation (not including within 48 hours of operation)	17	4, infarcted bowel 4, carcinomatosis 3, cerebrovascular stroke following lymph node biopsy (1) and total hip arthroplasty (2) 2, myocardial infarction following hip pinning 1, ruptured abdominal aortic aneurysm 1, gangrenous gallbladder 1, pulmonary embolis following hemicolectomy 1, pulmonary hemorrhage from bronchiectasis

* Major underlying disease process or cause of death is identified.

anesthesia. The primary anesthetic technique in the remainder included regional in 17%, intravenous (I.V.) sedation with or without local anesthesia in 15%, and local anesthesia in 21%. This distribution of anesthetic techniques was dictated largely by the surgical procedures performed (Table 4). Sixty-three per cent of the procedures involved the gastrointestinal (GI) (including hernias), genital, or musculoskeletal systems. Operations for fractures accounted for 25% of all surgical procedures. This finding is related to the observation that 26% of all operations were for trauma and that 19% were emergency operations.

Despite the significant nature of many of the surgeries and the prevalence of chronic disease, these elderly Olmsted County residents faired quite well. Ninety-two per cent were discharged from the hospital alive following surgery. Of the 28 deaths within 30 days, seven occurred intraoperatively and four others within 48 hours of operation (Table 5). While survival was slightly impaired immediately following surgery when compared with expected values for the general population of like age and sex (Fig. 2), the estimated survival at the end of 1 year was 74%, the same as expected. For years 2 through 5, the cumulative observed survival was slightly better than expected so that by 5 years after the initial surgery, the observed survival was estimated at 23% compared to an expected 17%.

Discussion

We have observed that the rate of surgical procedures on patients ≥ 90 years of age increased nearly fivefold between 1975 and 1978, and then seemed to level off somewhat. The cause of this increase and plateau is unclear. The abrupt increase may have coincided with the widespread use of a new surgical procedure, such as total hip arthroplasty or lens implant, that would have been commonly used in this age group. We were not, however, able to identify such procedures in our patient population (Table 6). Another change in medical practice during this period was the more liberal use of perioperative invasive monitoring. This change may have influenced surgeons to operate on sicker (and frequently older) patients. We are not able to address this hypothesis with our data.

Using 1987 U.S. Census projections, there exists a potential for nearly 91,000 operations in this age group each year if the annual rate of 89.0 per 1000 for the final 8 years of the study is applied to the entire U.S. population of this age. As surgical indications for these extremely elderly individuals are liberalized throughout the country, care will be even more expensive for this rapidly growing segment of the population.

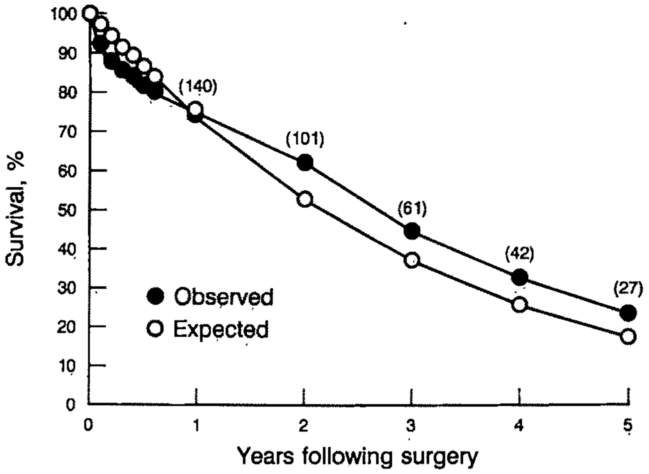

FIG. 2. Survival of 224 Olmsted County, Minnesota residents ≥ 90 years of age following surgery (1975–1985). For patients with multiple surgeries ≥ 90 years of age, only the first surgery was used, and time 0 is the date of first surgery. The number of persons alive and being followed at yearly intervals is given in parentheses.

Using a geographically defined community population for study, we avoided the distortions of referral bias.[11,12] Referral patients do provide the bulk of our surgical workload, however, so that no inherent temptation exists to increase operative rates in the local population. Moreover, all physicians in our practice are salaried with no financial incentives or disincentives for deciding to use a procedure. Although these considerations do not insure optimal practice, nonmedical considerations in the surgical decision process are minimized.[13]

Estimates based on the Olmsted County population do have several potential disadvantages, however. There are very few nonwhite residents; if surgical utilization rates differ for white and nonwhite people ≥ 90 years of age, Olmsted County estimates cannot be applied to the nonwhite population nationally. The Olmsted County rates might also provide an underestimate if there is greater per capita performance of surgery in major metropolitan areas. Although the proportion of urban residents in Olmsted County (71%) is the same as that nationally, Rochester is a small city and surgical rates may not be entirely applicable to larger cities.[14] Finally, our projection underestimates the incidence of operations if indications for surgery in this age group are liberalized further.

Liberalization of indications is influenced, in turn, by the outcome of surgery. One might have expected poor survival in these individuals because chronic diseases were so common[15]; 85% were ASA Class 3 or greater. This scale has been demonstrated to be applied with remarkable consistency by different groups of anesthesiologists.[16] Although not intended as a predictor of perioperative risk, several studies have demonstrated it to be a reliable predictor of overall outcome.[17,18] Despite the prevalence of chronic illness in this group, however, 92% were discharged from the hospital alive following surgery. When compared with peers from the general population, the modest increase in mortality rates in the first 6 months had reversed after 1 year, and, at 5 years, survival in the surgery group was somewhat higher than that expected.

The 9.3% 30-day postoperative mortality rate of our patients represents a marked improvement from reported mortality rates in this age group in the past two decades. Denney and Denson,[19] in 1972, reported on 272 patients ≥ 90 years undergoing procedures similar to our patients and in approximately equal ratios. They found a 30-day postoperative mortality rate of 29%. Interestingly, the major causes of death in their series were pneumonia and atherosclerosis with myocardial infarction. We did not find either to be a major cause of death (Table 5). This enhanced early survival may be due to surgical and anesthetic advances and improved medical care. We were not, however, able to demonstrate an improvement in mortality rate over the 10-year period of our study.

TABLE 6. *Procedure Frequency versus Calendar Years in Men and Women Combined (Selected Procedures with ≥20 Procedures Done over Entire Study)*

	1975–1978		1979–1982		1983–1985	
Procedure	N	Rate*	N	Rate*	N	Rate*
All musculoskeletal	25	22.2	37	27.1	35	28.1
Hip and pelvis including fracture	19	16.8	26	19.0	28	22.5
All digestive	19	16.8	31	22.7	35	28.1
Bowel, rectal, anal	6	5.3	14	10.2	6	4.8
All cardiovascular	7	6.2	17	12.4	9	7.2
Pacemaker insertion	6	5.3	13	9.5	5	4.0
Eye, lens surgery including cataract	5	4.4	10	7.3	20	16.1

* Crude annual incidence per 1000.

In summary, we have seen both an absolute and relative increase in surgical utilization in this age group. The population 90 years of age and over is growing, the perioperative mortality rate is not markedly different from the mortality rate in the general peer group, and survival may be enhanced by surgical intervention. Increasing rates of surgery in this group, combined with improved survival of operated patients, may have a significant impact on health care costs. Although a formal cost analysis is beyond the scope of this study, these findings may provide information useful in evaluating future needs for health care resources.

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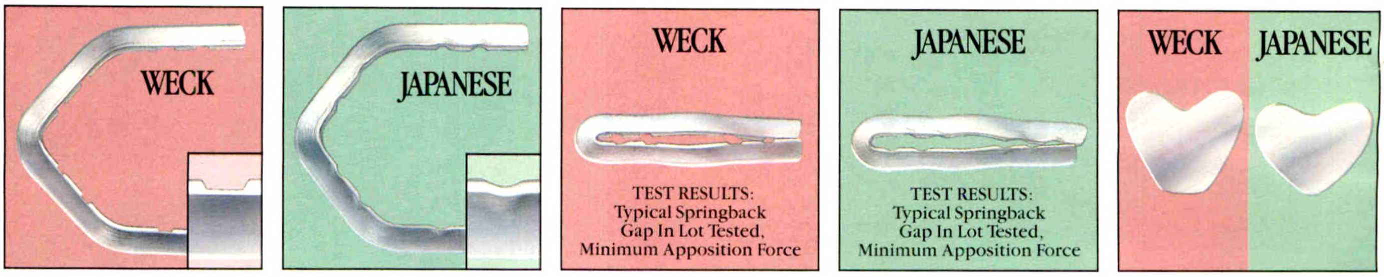
We make the Hemoclip® clip like it is because of the way nature made blood vessels.

Hemoclip® ligating clips are made for blood vessels.

That sounds obvious, but it's not to everyone.

It's not easy to make ligating clips that are finely balanced between strength and malleability–two desirable ligating clip properties.

But in a quarter-century of manufacture, Weck has learned to do the job on this key implant device as no one else has.



The Hemoclip® ligating clip is coined with distinct rectangular transverse grooves, designed for longitudinal gripping power. Clip wire is processed metallurgially for malleability in closure. The Japanese imitation clips have shallow-drawn wire, and smaller, rounded transverse grooves. Deeper Hemoclip® wire shape aids retention in Weck appliers. (Typical closure illustrated from independent study.)

But now there's a problem you should be aware of. Some U.S.-based companies have begun distributing–not manufacturing–Japanese imitations of the Hemoclip® ligating clip. These clips are not the product of Weck manufacturing expertise and the technical performance of these clips is simply not the same as that of Hemoclip® ligating clips, an exclusive Weck product.

They may look the same, but they're not.

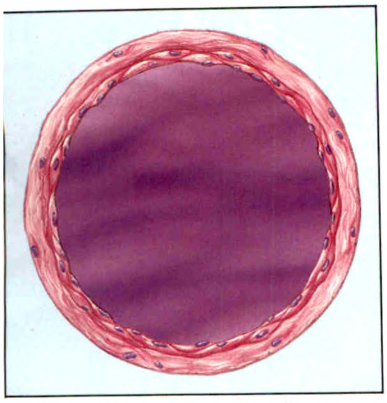
The recently-introduced Japanese clips look the same as Hemoclip® ligating clips to the naked eye. But a recently completed independent lab study of sample quantities of clips confirms Weck's own observation of substantial differences in closure properties between the Japanese clips and Weck clips.

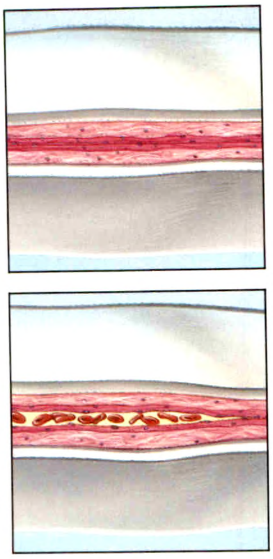
Vessel walls may be as thin as one-twelfth of vessel diameter.

Veins, in contrast to arteries, have very thin walls. When you consider that the vein tributaries ligated in surgery are sometimes one millimeter in diameter or smaller, with combined vessel walls as small as seven-thousandths of an inch (178 microns), according to animal studies on comparable vessels, you can appreciate the functional importance of differences in closure gap.

Arterial tributaries can be tiny, too, and although their walls are generally thicker than vein walls, arterial pressure is higher than venous pressure.

It seems prudent to employ ligating clips which offer the response and clip-closure performance Weck usage has established in your surgery.

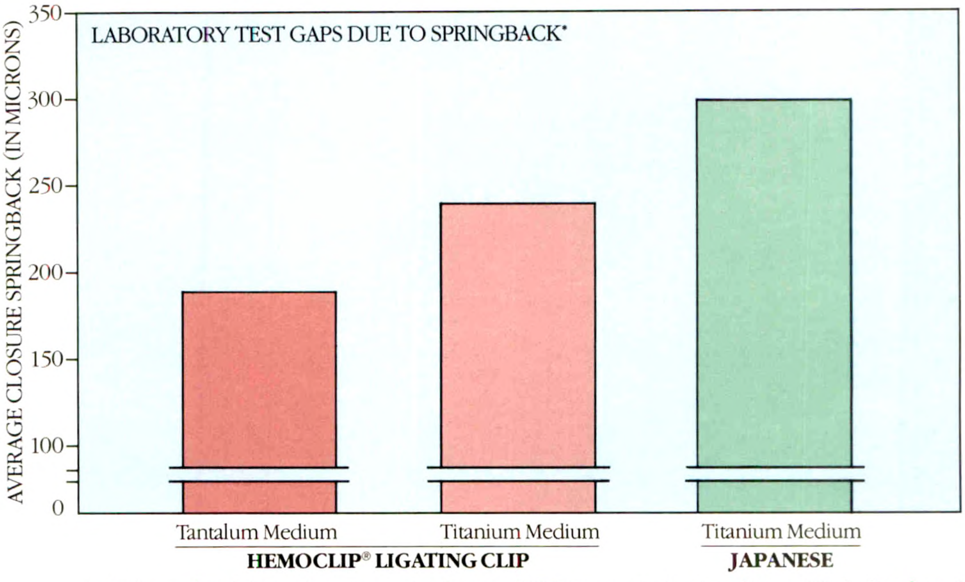




ABOVE. A vein tributary of 1mm can have a combined wall thickness of just seven-thousandths of an inch (178 microns), according to animal studies. RIGHT. A ligating clip that demonstrates greater springback than the clip you have regularly used for such vessels may be more likely to leave a closure gap larger than the vessel-wall thickness of a tiny vessel.

Weck's titanium clip vs. their titanium clip. A 23-27% difference.

Examine the chart for a visual representation of the difference in closure springback an independent research firm discovered between a set of Weck titanium medium-size clips and a set of Japanese titanium medium-size clips obtained directly from U.S. distributors of those clips. Both sets of clips were closed in Weck appliers through use of force-control devices.



An independent lab study on two sample sets of 25 Japanese imitation clips vs. Weck clips found that the Japanese medium-size clips, closed to initial complete touching of clip legs, evidenced mean closure gaps, due to springback, 23-27% larger than Weck medium-size titanium clips, and 56-61% larger than Hemoclip® tantalum clips from Weck. Other sizes produced similar results. (Closure gap in microns-one micron = one thousandth of one millimeter).

Closure of two sample sets of 25 Japanese titanium medium clips at forces adequate to achieve initial complete touching along clip legs resulted in closures of about 12 thousandths of an inch (305 microns) for the Japanese clips, 23-27% larger than the Weck titanium clip closure gap.

Weck's tantalum clips vs. their titanium clips. A 56% springback difference.

The comparison of Japanese titanium with Weck tantalum clips is even more important.

The Japanese companies make only titanium clips, and so they have sold hard on the benefits of titanium.

Tantalum is a softer material known for excellent clip closure. And the study revealed 56% and 61% larger mean closure gaps after springback for two sets of Japanese titanium clips, a ringing endorsement of the closure advantages of the Weck tantalum clips tested.

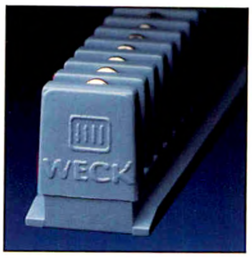
**Stronger closure forces would likely be employed during actual surgery cases.*

The comparison was similar for Weck stainless vs. Japanese titanium, with the stainless scoring substantially smaller gaps after springback.

Odds are, if you are using Weck clips you are accustomed to tantalum or stainless steel clip closure, because the vast majority of Weck accounts use these two metals.

And a new Weck-funded NMR major-university study indicates that magnetic deflection of tantalum clips is negligible, just as it is for titanium clips. So if your local competitive salesman distributing Japanese clips tries to convince you that titanium clips are exclusively acceptable for NMR magnetic deflection in preference to tantalum, we suggest you cite the new Weck-sponsored university study.

Look for the Weck name on the cartridge.



To visually and quickly confirm that you really are using Weck clips, look at the end of the clip cartridge. If you are using Weck clips, you should see there the Weck name molded into the plastic. The Weck name is your assurance of genuine Hemoclip® clip processing experience and knowledge.

Perfection In A Surgeon's Hand.™ **WECK**®
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If you would like more detailed information on any of the points covered here, write Edward Weck Incorporated, P. O. Box 12600, Research Triangle Park, NC 27709. 1-800-334-8511. In NC 1-800-672-6583.

Effect of T Cell Modulation on the Translocation of Bacteria from the Gut and Mesenteric Lymph Node

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Although the ability of the gut-associated lymphoid tissue (GALT) to respond to orally ingested foreign antigens has been studied extensively, its function in preventing or limiting escape of resident gut bacteria has not been assessed. The following studies were performed to examine what role cell-mediated immunity (CMI) plays in this process. The ability of suppression of CMI to induce escape of gut bacteria (translocation) to the mesenteric lymph node (MLN) in immunocompetent mice whose gut flora was unaltered was examined. Administration of cyclosporine or anti-L3T4 antibody failed to induce translocation of indigenous gut bacteria after 7 or 14 days of treatment. Antithymocyte globulin (ATG) also failed to induce translocation after 7 days of treatment, despite depletion of all Thy 1, Lyt 1, L3T4, and Lyt 2 positive cells from the spleen, MLN, and intestine as demonstrated by immunofluorescent microscopy. Finally, cultures of the MLN, spleen, liver, and peritoneum of T cell-deficient BALB/c nude mice and their heterozygous T cell-replete littermates were also sterile, demonstrating that congenital suppression of T CMI also does not lead to translocation of indigenous gut bacteria. The role of CMI in limiting systemic spread of bacteria that were already translocating to the MLN was also examined. Translocation of *Escherichia coli* C25 to the MLN was induced by gastrointestinal (GI) monoassociation, which leads to translocation of *E. coli* C25 to the MLN in 80–100% of mice. Treatment with ATG during monoassociation failed to induce spread of *E. coli* C25 to the spleen, liver, or peritoneum, despite the same degree of T cell depletion achieved with ATG in the previous experiment. Monoassociation of conventional T cell-deficient BALB/c nude and heterozygous mice and germ-free T cell-deficient BALB/c nude and heterozygous mice also did not lead to spread of *E. coli* C25 beyond the MLN. However, in ATG-treated, conventional nude, and germ-free nude mice, the average number of translocating *E. coli* C25 per MLN was consistently higher. In separate experiments the ability of stimulation of T cell function to inhibit translocation of *E. coli* C25 was examined. Recombinant interleukin-2, 25,000 units, was administered intraperitoneally every 8 hours during exposure to *E. coli* C25. This reduced the incidence of translocation of *E. coli* C25 from 85% to 51% (p = 0.02). Suppression of CMI, either systemically or within the GALT, has a minimal influence on the mechanisms by which the normal gut flora are translocated to the MLN. However, suppression of CMI promotes increased survival of the bacteria that have translocated to the MLN. Conversely, augmentation of T cell function may reduce the number of bacteria that survive in the node, possibly by enhanced bacterial killing within the local environment of the MLN.

HOSPITAL-ACQUIRED or nosocomial infection continues to be one of the leading causes of death in critically ill surgical patients. Whether following trauma, burns, or routine intra-abdominal surgery, the majority of these infections are due to gram-negative bacilli, enterococci, *Candida albicans,* and coagulase-negative staphylococci. Coagulase-negative staphylococcal infections are most often due to colonization of intravascular monitoring devices. Infections caused by gram-negative bacilli, enterococci, and *C. albicans,* microbes that are normally found primarily in the gastrointestinal (GI) tract, appear at a variety of sites including the lung, peritoneal cavity, sinuses, and urinary tract. Recently, however, it has been recognized that the GI tract, due to an acquired inability to confine microbes, may also serve as a reservoir for systemic infection in these patients.[1] Because surgical patients frequently suffer from malnutrition, gram-negative infection, shock (with compromised mesenteric blood flow), ileus with its attendant stasis of intestinal contents, and lack of oral intake, the capability of the gut to maintain

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its mucosal and immune barriers against the escape of microbes (referred to as translocation), may be severely compromised. Since many of these predisposing factors are often found together, systemic escape of gut microbes or toxins may have important consequences in such critically ill patients.

Although all of these factors may lead to changes in gut structure and function, it is unknown what impact depression of immune function has on the GI tract's ability to prevent escape of bacteria. In particular, many abnormalities of T cell function occur following burns, trauma, and sepsis including decreased total T cell number, diminished responsiveness to the T cell mitogen PHA and to the lymphokine interleukin-2 (IL-2), and the generation of suppressor T cells. In burn patients the degree of depression of the T cell response to PHA has been shown to correlate with both the degree of burn injury and with the risk of developing infection and of dying from infection.[2] In preoperative patients, the status of their T cell function, as measured by skin testing to ubiquitous antigens, is highly predictive of the risk of developing a life-threatening postoperative infection and of the risk of death from sepsis.[3]

Because T cell function is intimately involved with many aspects of the immune response, and because depression of T cell function is strongly correlated with an increased risk of nosocomial infection after surgery or trauma, we became interested in the role of the T cell in the control of bacterial translocation from the GI tract. We performed the following studies to determine what role, if any, T cell immunity plays both in the normal process of confining bacteria to the gut and in the prevention of systemic dissemination of bacteria that have translocated to the lymph nodes that drain the GI tract.

Materials and Methods

Animals

Female Swiss Webster mice, 18–22 g (Bio-Lab Corporation, St. Paul, MN) were used in experiments involving administration of cyclosporine (CSA), anti-L3T4 antibody, and antithymocyte globulin (ATG) alone. Female BALB/c mice, 18 to 22 grams, (Department of Laboratory Medicine and Pathology mouse colony, University of Minnesota, Minneapolis, MN) were used in the experiments combining ATG and IL-2 administration with *E. coli* C25 monoassociation. Congenitally athymic nude (nu/nu) and heterozygous (nu/+) BALB/c mice, 8–11 weeks of age, were obtained from Life Sciences, Jacksonville, FL. Germ-free, 18–22 g, female BALB/c nude and heterozygous mice were housed and treated at the University of Wisconsin Gnotobiotic Laboratory, Madison, WI.

Bacteriologic Methods

After death, a swab culture of the peritoneal surface was taken and then the mesenteric lymph nodes (MLN), and, when indicated, the spleen and liver, were excised aseptically. The cecum was then removed, weighed, and transferred immediately to an anaerobic chamber (Forma Scientific, Marietta, OH). The MLN, spleen, and liver were homogenized with autoclaved glass stoppers in brain-heart infusion broth (Difco Laboratories, Detroit, MI) (MLN in 2 mL; spleen and liver in 4 mL). Two hundred microliters of the homogenate was plated in duplicate on 5% sheep blood agar (DiMed Inc, St. Paul, MN) and incubated at 35 C for 48 hours, after which the number of colony forming units (CFU) present per organ was determined. The peritoneal swab was incubated at 35° in 4 mL of brain-heart infusion broth for 24 hours following which 200 μL was plated in duplicate on 5% sheep blood agar and incubated at 35 C for 24 hours. Ceca were homogenized in 9 mL of prereduced Hank's balanced salt solution (Gibco Laboratories, Grand Island, NY). After serial dilution, 20 μL of each dilution was plated on each of the following media: (1) eosin-methylene blue agar (Difco) for enumeration of facultative gram-negative bacilli; (2) colistin-nalidixic acid agar (Difco) for enumeration of aerobic and facultative gram-positive bacteria; (3) Wilkins-Chalgren agar (Difco) supplemented with 0.1 mg/mL of gentamicin for enumeration of strictly anaerobic bacteria, and, where appropriate; and (4) nutrient agar (Difco) supplemented with 0.1 mg/mL of streptomycin sulfate (Sigma Chemical Co., St. Louis, MO) for enumeration of *E. coli* C25. After incubation for 24–48 hours, plates were read and total CFU/g of cecal weight was determined.

Gut Monoassociation with E. Coli *C25*

Mice were intestinally decontaminated by adding 2 mg/mL of streptomycin (Sigma) and 2 mg/mL of bacitracin (Sigma) to their drinking water for 4 days. An overnight culture of streptomycin-resistant *E. coli* C25 (provided by Dr. Rodney Berg, LSU Medical Center, Shreveport, LA) in brain-heart infusion broth (10^9 CFU/mL) was then added to the antibiotic-containing drinking water in a 1:1 dilution. Mice were killed after 48 hours of exposure to *E. coli* C25. In separate experiments, germ-free nude and heterozygous mice were orally inoculated with *E. coli* C25 without prior antibiotic treatment and 48 hours later were transferred by overnight air freight to our laboratory in shipping containers designed to maintain gonotobiotic conditions. The peritoneum, MLN, spleen, and liver were then cultured as described above.

Immunosuppressive Agents

Cyclosporine (CSA; Sandoz, Basel, Switzerland, 100 mg/mL) was diluted in olive oil to the desired concentration and administered subcutaneously in the flank once a day. CSA whole blood levels were determined by high pressure liquid chromatography by the Clinical Chemistry Laboratory, University of Minnesota Hospitals, Minneapolis, MN.

Anti-L3T4 antibody was derived from the GK1.5 monoclonal cell line (ATCC-TIB 507) from which antibody-rich supernatant was harvested and stored at −70 C. Aliquots were thawed just prior to use, and 0.5 mL of undiluted antibody supernatant or media control was injected daily into the dorsal tail vein. To determine the per cent of L3T4-positive cells remaining after 14 days of treatment, pooled cervical, axillary, inguinal, and MLN single-cell suspensions from three control and three L3T4-treated mice were incubated with anti-L3T4 antibody (1:2 dilution of monoclonal cell culture supernatant) and then counterlabeled with a 1:50 dilution of fluorescein-labeled antimouse immunoglobulin antibody (Cappel Laboratories, West Chester, PA) and then subjected to fluorescent activated cell sorter analysis to determine the percentage of L3T4-positive cells. The

TABLE 1. *Effect of CSA, Anti-L3T4 Antibody, and ATG on the Translocation of Indigenous GI Bacteria to the MLNs*

Treatment	Dose	No. of Mice with Translocation/Total No. of Mice* Day 7	Day 14
CSA	0	0/20	0/20
	10 mg/kg/d	1/20	0/20
	50 mg/kg/d	2/20	2/20
Anti-L3T4	0	1/10	1/10
	0.5 mL/d	1/10	1/9
ATG	0	2/20	ND
	1 mg/d	1/10	ND
	3 mg/d	3/10	ND
	6 mg/d	2/10	ND

* $p > 0.05$ for CSA, Anti L3T4, and ATG treatments compared to control by chi square analysis with a Yates continuity correction.
ND = not done.

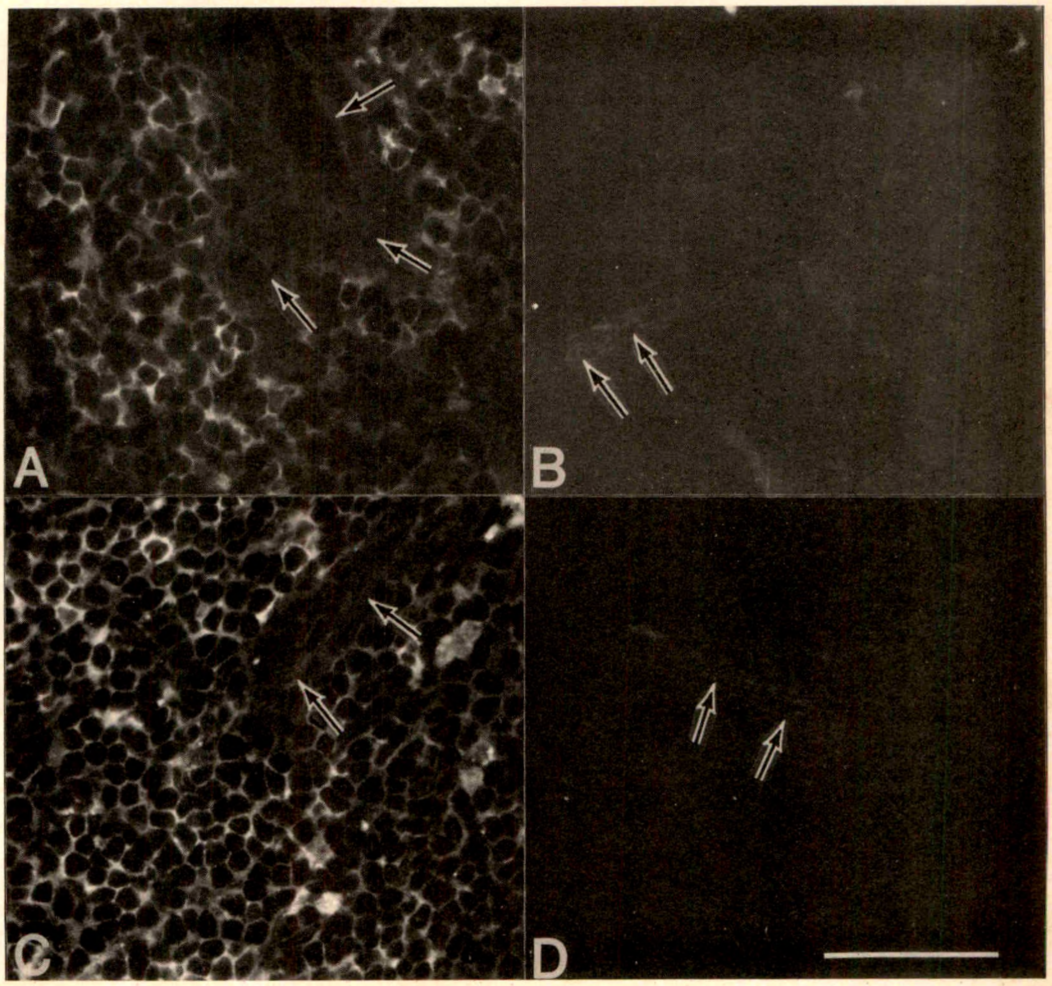

FIG. 1A–D. Frozen sections of spleen after staining with anti-Thy 1 (*A* and *B*) and with anti-Lyt 2 (*C* and *D*) (control: *A* and *C;* ATG-treated: *B* and *D*) demonstrating complete depletion of these cells. Staining with anti-L3T4 and anti-Lyt 2 antibodies also showed a complete absence of these T cell phenotypes. Scale bar represents 50 μm.

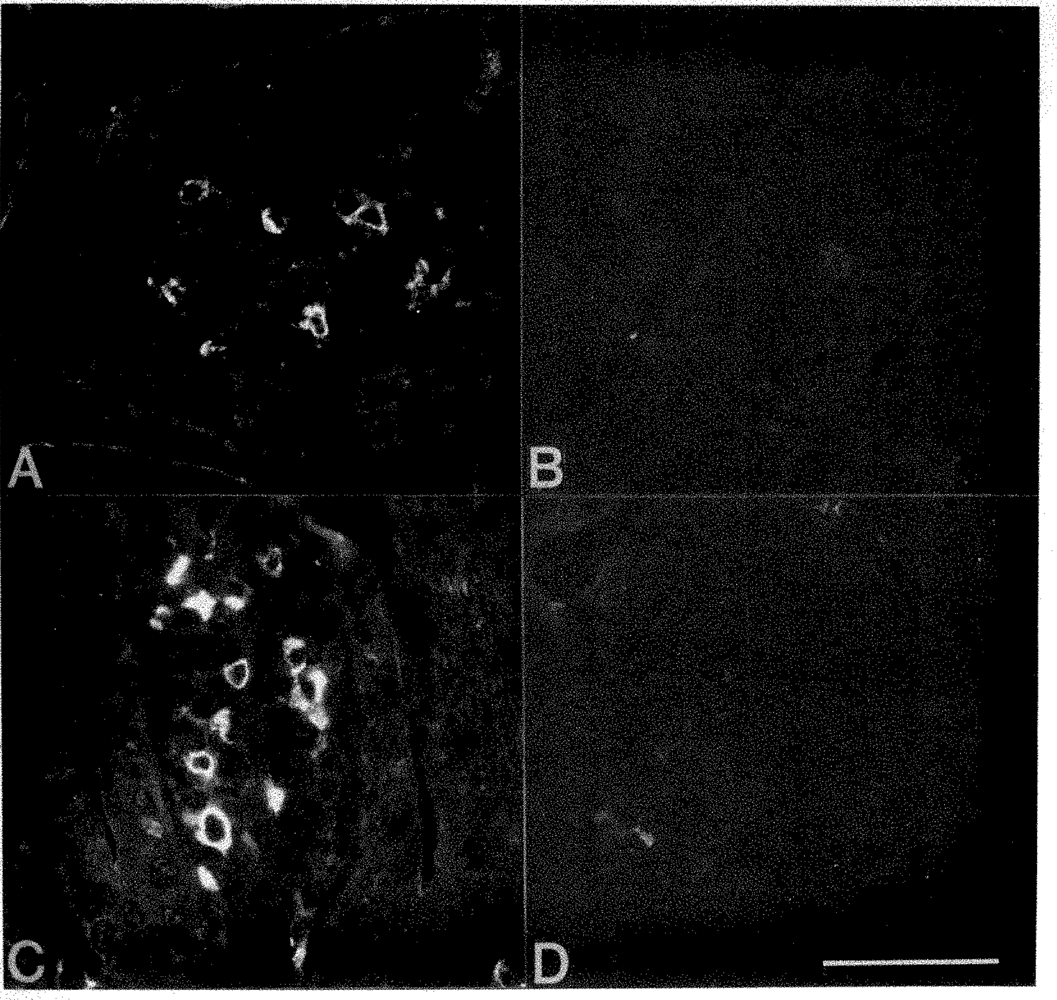

FIG. 2A–H. Frozen sections of small intestine after staining with anti-Thy 1 (*A* and *B*), anti-Lyt 1 (*C* and *D*), anti-L3T4 (*E* and *F*), and anti-Lyt 2 (*G* and *H*) (control: *A*, *C*, *E*, and *G*; ATG treated: *B*, *D*, *F*, and *H*, demonstrating complete depletion of these T cell phenotypes from the small intestine). Scale bar represents 50 μm.

average number of L3T4-positive cells remaining was expressed as a per cent of those found in control mice.

ATG (provided by Richard Condie, Director, Minnesota ALG Program, ALG Laboratories, Minneapolis, MN) is a pooled polyclonal IgG preparation derived from the immunization of horses with mouse thymocytes. The antibody was diluted in normal saline to the desired concentration, and 0.5 mL was administered intravenously (I.V.) daily via the dorsal tail vein.

IL-2 is a purified recombinant human lymphokine obtained from Cetus Corporation, Emoryville, CA. Appropriate dilutions were made in Hank's balanced salt solution without calcium or magnesium and administered intraperitoneally in a volume of 0.25 mL.

Immunofluorescent Antibody Studies

Tissues were snap frozen in precooled isopentane and stored at −70 C until used. Frozen tissue sections (4-μm thickness) prepared in a Lipshaw cryostat were stained using an indirect immunofluorescence technique previously described in detail.[4] Briefly, sections were fixed with acetone, washed in phosphate-buffered saline, and then reacted with an appropriately diluted monoclonal antibody and then reacted sequentially with the following: (1) affinity isolated fluoresceine isothiocyanate (FITC) F(ab′)2 conjugated goat-antirat IgG (H and L); (2) affinity isolated (FITC) F(ab′)2 rabbit antigoat IgG (H and L); and (3) p-phenylenediamine to retard fluorescence fading. FITC conjugated antibodies were absorbed with mouse serum prior to use. For each tissue, control sections were prepared as described above, omitting application of the monoclonal antibody.

Rat monoclonal antibodies were obtained from the following sources: anti-Thy 1 was obtained from Boehringer, Indianapolis, IN; anti-Lyt 1 (CD5) (53-7.3) and anti-Lyt 2 (CD8) (53-6.7) were from Becton Dickinson, Mountainview, CA; and anti-L3T4 (CD4) (GK1.5) was from ATCC. Antirat antibodies were from Pel-Freeze, Rogers, AR, and antigoat antibodies were from Cooper, Malvern, PA.

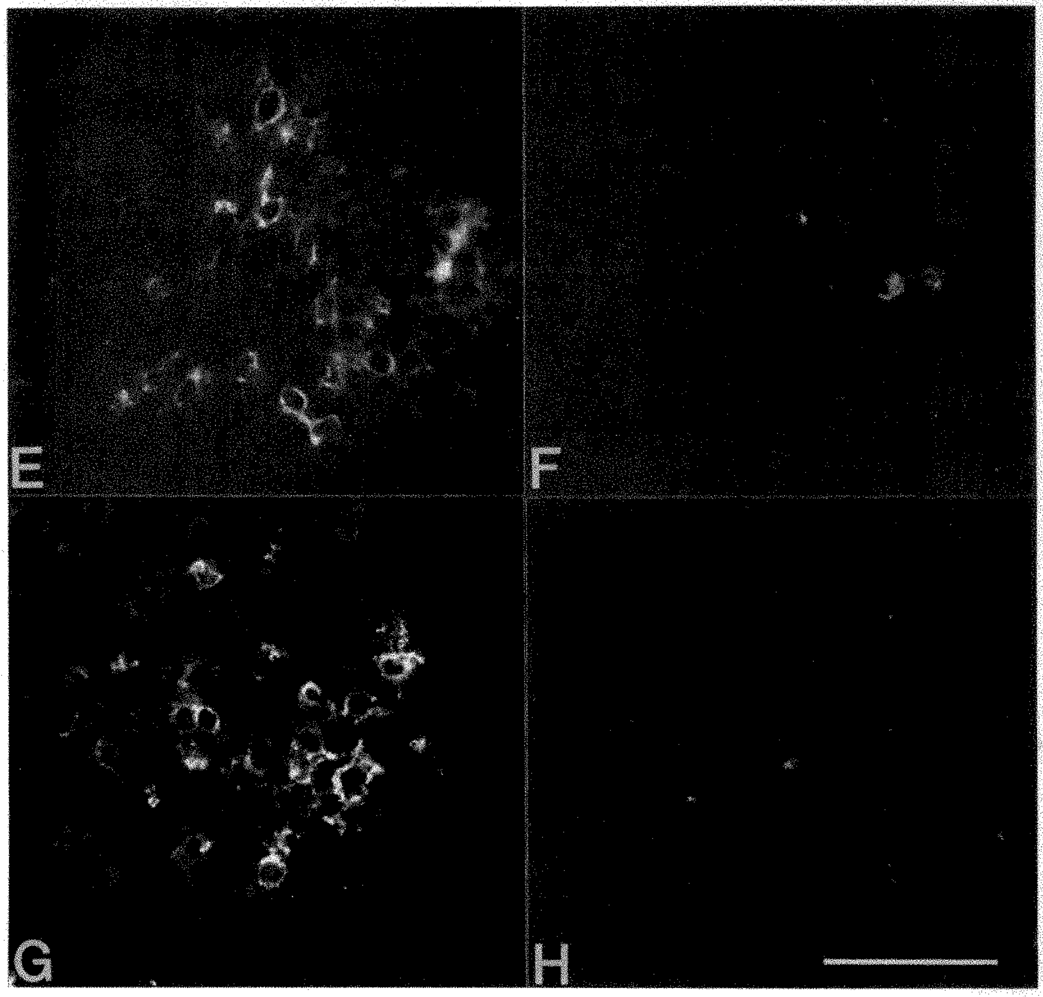

FIG. 2. (*Continued*)

Results

Effect of Suppression of Cell-mediated Immunity on Translocation in Immunocompetent Mice with a Normal Gut Flora

The first series of experiments was done to evaluate the ability of several T cell specific immunosuppressive agents to induce translocation from the gut to the MLN of Swiss Webster mice with a stable GI flora. In our laboratory, these mice exhibit a spontaneous translocation rate to the MLN of 0–10%. We first attempted to specifically suppress T-helper cell function through the use of CSA and anti-L3T4 antibody. CSA, which inhibits T-helper cell production of IL-2 and gamma interferon,[5] was administered daily in doses of either 10 mg/kg (a dose approximating that used for clinical organ transplantation) or 50 mg/kg (a more toxic dose). Control animals received olive oil devoid of CSA. On day 14 the average CSA whole blood level (taken 24 hours after the last dose) as determined by high pressure liquid chromatography was 160 ± 19 and 704 ± 67 mcg/liter (N = 3), respectively. Cultures of the MLN on days 7 and 14 demonstrated that translocation was not induced by CSA, despite moderate to high whole blood CSA levels (Table 1).

L3T4 is a cell surface molecule on mouse T-helper cells, which, through its interaction with class II major histocompatability antigens, facilitates recognition of foreign antigens.[6] Anti-L3T4 monoclonal antibody, when given *in vivo*, depletes the blood, spleen, and lymph nodes of L3T4 positive cells by 75–90% at 48 hours and 1 mg/wk can sustain a <90% reduction indefinitely.[7] In this experiment, 0.5 mL of undiluted hybridoma supernatant was administered I.V. daily for 14 days. Fluorescent activated cell sorter analysis of peripheral lymph node cells on day 14 demonstrated an average reduction of L3T4-positive cells of 75%. Cultures of the MLN on days 7 and 14 demonstrated that depletion of T-helper cells also failed to induce translocation (Table 1).

TABLE 2. *Incidence of Translocation of Indigenous GI Bacteria to the MLNs, Spleen, Liver, and Peritoneal Cavity of Athymic (Nude) Mice and Heterozygous (Thymic) Littermates*

	Site of Bacterial Translocation			
Type of Mouse	MLN	Spleen	Liver	Peritoneal Cavity
Heterozygote	2/20	0/20	0/20	0/17
Nude	0/18	1/18	0/17	1/16

Values are given as no. of mice with translocation of indigenous bacteria/total no. of mice.

TABLE 4. *Effect of ATG on the Incidence of* E. coli *C25 Translocation to Various Organs in Mice Monoassociated with* E. coli *C25**

	No. of Organs with Translocation of *E. coli* C25/Total No. of Mice			
Treatment	MLN	Spleen	Liver	Peritoneal Cavity
Monoassociation alone (control)	8/8	1/8	0/8	1/8
Monoassociation + ATG	8/8	0/8	0/8	ND

* BALB/c mice with a conventional cecal microflora were gut decontaminated for 4 days with oral bacitracin and streptomycin sulfate and were then orally monoassociated with *E. coli* C25 for 2 days; 3 mg/d of ATG was given over this 6-day period, and the organs were cultured on day 7.

Since neither T-helper cell inhibition (CSA) nor depletion (anti-L3T4 antibody) induced translocation, we next sought to more broadly deplete the animals of T cells with ATG. In our laboratory, when used as the sole immunosuppressive agent in mice, four 0.5 mg doses of ATG prevent rejection of skin grafts across major histocompatability barriers for an average of 25 days. One, three, and six mg of ATG was given I.V. daily over 7 days at which time the MLN were cultured. To assess the degree of T cell depletion induced by ATG, sections of the spleen, MLN, and small intestine of control animals and those given 3 mg ATG/day (N = 3) for 7 days were examined by immunofluorescent microscopy using fluorescein-labeled monoclonal antibodies to the cell surface antigens Thy 1, Lyt 1, L3T4, and Lyt 2 (Figs. 1 and 2). These studies demonstrated that this dose of ATG completely depleted these T cell phenotypes from the spleen and small intestine. Identical results were obtained from spleens stained with anti-L3T4 and anti-Lyt 2 and for MLN stained with anti-Thy 1, anti-Lyt 1, anti-L3T4, and anti-Lyt 2. To ensure that the administered ATG was not simply binding *in vivo* to the cell surface antigen and therefore blocking the binding of the fluorescein tagged monoclonal antibodies, sections of spleen from control animals were exposed to a 1:10,000 dilution of ATG and then stained with a fluorescein-labeled monoclonal antihorse-Ig antibody. Sections of spleen from ATG treated animals were stained only with the antihorse-Ig antibody. Sections from control animals demonstrated intense fluorescence whereas those from ATG-treated animals had no fluorescence (not shown), demonstrating that actual depletion of T cells did occur. However, despite such a profound depletion of T cells from both the systemic T cell pool and the GALT, a significantly increased incidence of translocation was not induced at any of the doses of ATG used (Table 1).

Cecal flora studies showed no effect of CSA, anti-L3T4, or ATG on the number of gram-positive, gram-negative, or anaerobic bacteria per gram of cecum (data not shown).

Translocation of Indigenous Gastrointestinal Bacteria in Nude Mice

To assess whether T cell-deficient nude mice have an intrinsic defect in the ability of their GI tract to prevent translocation, the MLN, spleen, liver, and peritoneum were cultured in heterozygous (nu/+) and nude (nu/nu) littermates without prior intestinal flora manipulations. Table 2 shows that translocation of indigenous gut bacteria to the MLN, liver, spleen, or peritoneum in either heterozygous or nude mice was not occurring. However, an unexpected finding was that the cecal flora differed quantitatively from that found in Swiss Webster mice of comparable age (Table 3). The normal level of facultative gram-negative bacteria was significantly lower in the heterozygous and nude mice compared to the higher level observed in the Swiss Webster mice. Total anaerobic and gram-positive bacteria, however, were similar. This may partially account for the lack of translocation of gram-negative bacteria in the immunodeficient nude mice.

TABLE 3. *Average Log_{10} ± SE Viable Bacteria per Gram of Cecum in Conventionally Reared Swiss Webster Mice, in Balb/c T Cell-deficient (Nude) mice, and Their Heterozygous (Thymic) Littermates*

Type of Mouse	Strict Anaerobes	Aerobic and Facultative Gram-positive Bacteria	Aerobic and Facultative Gram-negative Bacilli	Average Cecal Weight (g)
Heterozygote (N = 4)	10.3 ± 0.3	7.4 ± 0.7	3.7 ± 1.0	0.72 ± 0.07
Nude (N = 4)	9.7 ± 0.5	7.4 ± 0.4	3.7 ± 1.0	0.56 ± 0.10
Swiss Webster (N = 4)	9.2 ± 1.4	6.9 ± 0.6	6.7 ± 1.7	0.50 ± 0.20

TABLE 5. *Effect of ATG on the Cecal Bacterial Counts of Mice Monoassociated with* E. coli *C25**

	Average Log_{10} ± SE Cecal Bacteria per Gram (N = 4)			
Treatment	*E. coli* C25	Strict Anaerobes	Aerobic and Facultative Gram-positive	Average Cecal Weight (g)
Monoassociation alone (control)	9.7 ± 0.3	0	1.0 ± 0.1	1.0 ± 0.1
Monoassociation + ATG	9.8 ± 0.1	0	1.03 ± 0.1	1.0 ± 0.1

* BALB/c mice with a conventional cecal microflora were gut decontaminated for 4 days with oral bacitracin and streptomycin sulfate and were then orally monoassociated with *E. coli* C25 for 2 days; 3 mg/d of ATG was given over this 6-day period, and the organs were cultured on day 7.

Effect of T Cell Deficiency on the Translocation of E. coli *C25*

Since neither T cell inhibition (CSA) or depletion (anti-L3T4, ATG, nude mice) induced translocation in mice with a normal intestinal flora, the influence of T cell immunity on translocation was next examined in mice monoassociated with *E. coli* C25. By decontaminating the GI tract with oral bacitracin and streptomycin for 4 days and then adding streptomycin-resistant *E. coli* C25 to the drinking water for 2 days, intestinal overgrowth of *E. coli* C25 to abnormally high levels occurs. Such intestinal overgrowth (monoassociation) leads to translocation of *E. coli* C25 to the MLN in 80–100% of animals but not to other organs.[8] Therefore, in animals with intact host defenses, the MLN is the point at which translocation is contained. To test the hypothesis that depression of T cell immunity would impair the ability of the MLN to contain translocating bacteria, immunocompetent BALB/c mice were given 3 mg/d of ATG during the 6-day period of monoassociation with *E. coli* C25 (total of six doses). Control mice received saline injections. On day 7 the MLN, spleen, liver, and peritoneum were cultured and the incidence of translocation of *E. coli* C25 to each organ was determined. Immunofluorescent antibody studies of the spleen, MLN, and intestine (N = 3 for control and ATG-treated mice) were also repeated and showed the same degree of depletion of Thy 1, Lyt 1, L3T4, and Lyt 2 cells as shown in Figures 1 and 2.

Table 4 shows that treatment with ATG had no influence on the incidence of translocation of *E. coli* C25 to the MLN when compared with control animals. In addition, complete depletion of the systemic and GALT T cell pool did not promote spread of *E. coli* C25 beyond the MLN to the spleen, liver, or peritoneum. Since the cecal levels of *E. coli* C25 were the same in both control and ATG-treated animals (Table 5), both groups had an equal susceptibility to translocate.

To further evaluate the ability of the suppression of T cell function to promote spread of translocating bacteria, we next studied BALB/c nude mice with a normal gut flora (conventional) and germ-free BALB/c nude mice. Conventional BALB/c nude mice and their heterozygous littermates were monoassociated with *E. coli* C25 as above. Cultures of the MLN, spleen, liver, and peritoneum on day 7 again showed the expected translocation of *E. coli* C25 to the MLN, but again, no spread of *E. coli* C25 to the spleen, liver, or peritoneum was observed (Tables 6 and 7).

Germ-free mice, because they are isolated from the external environment from birth, have a sterile GI tract. Therefore, oral inoculation with *E. coli* C25 without prior antibiotic treatment leads to intestinal overgrowth and translocation to the MLN in 90–100% of the animals. Although translocation to the MLN reliably occurs in immunocompetent germ-free mice, spread of *E. coli* to the spleen, liver, or peritoneum does not.[9] To assess whether GALT T cell immunity is important in the generation of a protective immune barrier to the systemic escape of bacteria, germ-free nude mice and their heterozygous littermates were orally monoassociated with *E. coli* C25 for 2 days and on the third day the MLN, spleen, and liver were cultured. Despite the presence of extremely high levels of *E. coli* C25 in the ceca of both the heterozygous and nude mice, translocation was again confined to the MLN alone (Tables 8 and 9).

Although spread of *E. coli* C25 beyond the MLN did not occur in either the ATG-treated, conventional nude,

TABLE 6. *Effect of Monoassociation with* E. coli *C25 in T Cell-deficient BALB/c Nude Mice**

	No. of Organs with Translocation of *E. coli* C25/Total no. of Mice			
Type of Mouse	MLN	Spleen	Liver	Peritoneal Cavity
Heterozygote	4/7	1/7	0/6	0/7
Nude	7/7	0/7	0/7	0/7

* BALB/c T cell deficient nude mice and their heterozygous littermates were gut decontaminated for 4 days with oral bacitracin and streptomycin sulfate and were then orally monoassociated with *E. coli* C25 for 2 days. On day 7 the organs were cultured.

TABLE 7. *Cecal Bacterial Counts in T Cell-deficient Nude Mice and Their Heterozygous Littermates after Monoassociation with* E. coli *C25*

	Average Log_{10} ± SE Cecal Bacteria per Gram			
Type of Mouse	*E. coli* C25	Strict Anaerobes	Aerobic and Faculatative Gram-positives	Average Cecal Weight (g)
Heterozygotes (N = 4)	10.8 ± 0.4	1.9 ± 2.1	4.5 ± 0.5	0.88 ± 0.02
Nude (N = 3)	10.6 ± 0.3	1.4 ± 2.4	4.7 ± 0.3	0.69 ± 0.14

or germ-free nude mice, a consistent finding in all three experiments was that the average number of *E. coli* C25 per MLN was higher than that in control animals (Table 10).

Effect of Treatment with Interleukin-2 on Translocation of E. coli *C25*

To examine the influence of augmented cellular immune function on bacterial translocation, BALB/c mice were monoassociated with *E. coli* C25 and during the 2 days of oral exposure to *E. coli* C25, IL-2 was given intraperitoneally either every 8 hours (25,000 units per dose, total of six doses) or as a single bolus dose of 150,000 units on either the first or second day of exposure to *E. coli* C25. Cultures of the MLN showed that IL-2 significantly decreased the overall incidence of translocation of *E. coli* C25 to the MLN compared to control animals only when given every 8 hours. Giving IL-2 as a bolus of 150,000 had no effect on either the incidence or number of *E. coli* C25 per MLN (Table 11).

Discussion

Despite the continuous exposure of its epithelial surface to the hostile microbial environment of its lumen, the GI tract maintains a highly effective barrier to the systemic entrance of gut microbes. Since the composition of the normal cecal and ileal flora consists of approximately 10^{10} anaerobic bacteria/g, 10^{5-7} aerobic and facultative gram-negative bacteria/g, and 10^{6-8} aerobic and facultative gram-positive bacteria/g, this barrier must be relatively nonselective and indifferent to the extreme degree of microbial and antigenic diversity. On the other hand, it must also be capable of selectively responding to microbial pathogens that use the gut as their portal of entry.

The GI tract's defense against translocation appears to involve two components. The first is a nonspecific mechanical and chemical barrier. This is composed of the lining mucosal cells with their tight intercellular junctional complexes, the mucus layer, which overlays the epithelium, and, finally, the indigenous gut bacteria, particularly the anaerobic component. The large population of anaerobes normally present appears to play a particularly important role in the normal control of other resident gut bacteria.[10] Due to their high numbers, they prevent overgrowth of other gram-negative and gram-positive bacteria within the intestine and, by secreting large amounts of short chain fatty acids within the mucus layer overlying the epithelium, they inhibit the adherence of other potential pathogens, such as *C. albicans.*[11]

The second component of the GI tract's defense system is the immunologic defense or gut-associated lymphoid tissue (GALT). The GALT is composed of: (1) a diffuse population of T-helper cells, B cells, and plasma cells located throughout the lamina propria of the intestine, and (2) Peyer's patches (in the small intestine) and lymphoid nodules (in the small and large intestine). Although Peyer's patches and lymphoid nodules differ in size, both are histologically and functionally similar.[12] Their luminal surface is lined by a specialized phagocytic cell referred to as an M (for microfold) cell.[13] Below the M cell is a population of macrophages and below these are lymphoid follicles that are composed of T and B cells (Fig. 3).

TABLE 8. *Effect of Monoassociation on Translocation of* E. coli *C25 in Germ-free T Cell-deficient BALB/c Nude mice and Their Heterozygous Littermates**

	No. of Organs with Translocation of *E. coli* C25/Total No. of Mice		
Type of Mouse	MLN	Spleen	Liver
Germ-free heterozygote	9/10	0/10	0/10
Germ-free nude	8/10	0/10	1/10

* Mice were orally monoassociated with *E. coli* C25 for 2 days, and on day 3 the organs were cultured.

TABLE 9. *Cecal Counts ± SE of* E. coli *C25 in Germ-free T Cell-deficient Nude Mice and Their Heterozygous Littermates after Oral Monoassociation with* E. coli *C25 for 2 Days*

Type of Mouse	Average Log_{10} *E. coli* C25 per Gram of Cecum	Average Cecal Weight (g)
Germ-free heterozygotes (N = 4)	12.2 ± 0.2	0.78 ± 0.04
Germ-free nude (N = 4)	12.2 ± 0.2	0.59 ± 0.03

By virtue of their unique structure, Peyer's patches and lymphoid nodules serve as the focal point for the induction of immune responses to foreign antigens. After uptake of a foreign antigen by an M cell, it is transferred without alteration to the underlying macrophages. The macrophages are thought to process the antigen, present it to the lymphocytes of the surrounding lymphoid nodules, following which antigen-specific T and B lymphoblasts are generated. These cells leave the intestine, pass through the systemic circulation, and then *home* to the lamina propria of the intestine where they mature to T-helper/inducer cells, B cells, and plasma cells, which are committed to the secretion of antigen-specific IgA into the intestine (Fig. 4).[12] Despite the presence of such an elaborate system for the generation of luminal IgA, the presence of IgA does not appear to be essential for the maintenance of an immunologic defense against translocation of indigenous gut bacteria because patients with selective IgA deficiency do not have an increased incidence of infections caused by the bacteria normally found in the gut.[14] However, IgA is extremely important in the defense against pathogens, which have the gut as their target organ (*e.g.*, *Shigella* sp).[15]

Despite the presence of the both the mechanical/chemical barrier and the GALT, systemic translocation of indigenous gut bacteria does occur under a variety of circumstances. Escape of bacteria to the liver via the portal venous system appears to occur only when there has been an extreme insult (such as intestinal ischemia) to the integrity of the intestine.[16] However, translocation of bacteria from the gut lumen to the draining mesenteric lymph nodes can occur without direct damage to epithelial integrity. Van der Waaij et al. first noted in 1972 that the administration of oral antibiotics to mice would lead to translocation of bacteria to the MLN.[17] Since then it has been shown that disruption of the normal gut flora by the administration of selective antibiotics allows overgrowth of the remaining bacteria within the intestine and that such bacterial overgrowth often leads to translocation to the MLN.[18]

Translocation of indigenous gut bacteria to the MLN also occurs after a variety of other insults, such as following the administration of lipopolysaccharide,[19] after large body surface area burns,[20] with physical disruption of the gut mucosal barrier,[21] and after the administration of prednisone and cyclophosphamide.[22] Many of these situations have as part of their pathophysiology alterations in intestinal blood flow (LPS, burns with loss of fluid) or cellular function (cyclophosphamide), both of which can damage the integrity of the GI tract. Although the maintenance of an intact epithelial layer is critical in preventing translocation, the role of the GALT, in particular the role of T cell immunity, in the defense against translocating bacteria is unknown.

TABLE 10. *Effect of T Cell Deficiency on the No. of Translocating* E. coli *C25 Within the MLNs of Mice Monoassociated with* E. coli *C25*

Group Monoassociated with *E. Coli* C25	Average No. (±SE) *E. Coli* C25 per MLN	P Value*
ATG-treated		
Saline (N = 8)	21 ± 4	0.02
ATG (N = 8)	68 ± 16	
Conventional nude		
Heterozygotes (N = 7)	11 ± 6	0.07
Nude (N = 10)	40 ± 20	
Germ-free nude mice		
Heterozygotes (N = 10)	36 ± 8	0.15
Nudes (N = 10)	65 ± 17	

* Wilcoxon rank sum test.

In these studies we first sought to determine whether T cell dysfunction would induce translocation of indigenous gut bacteria in mice with a conventional cecal flora. Neither T-helper cell inhibition (CSA) or depletion (anti-L3T4 antibody), nor depletion of other T cells such as Lyt 2+ cells (T cytotoxic/suppressor cells) with ATG induced translocation. Because these alterations of T cell function were on a short-term basis (over a maximum of 14 days), the incidence of translocation to the

TABLE 11. *Effect of IL-2 on the Translocation of* E. coli *C25 to the MLN**

IL-2 Protocol	No. of Mice with Translocation of *E. coli* C25 to the MLN/ Total (%)	P Value†
Group I: 25,000 units every 8 hours		
HBSS	22/26 (85)	0.02
IL-2	14/27 (52)	
Group II: 150,000 units on day 1		
HBSS	10/10 (100)	NS
IL-2	10/10 (100)	
Group III: 150,000 units on day 2		
HBSS	8/9 (89)	NS
IL-2	9/10 (90)	

* BALB/c mice with a conventional cecal microflora were gut decontaminated for 4 days with oral bacitracin and streptomycin sulfate and were then orally monoassociated with *E. coli* C25 for 2 days. During the 2 days of oral *E. coli* C25 monoassociation mice received 150,000 units of IL-2 as: 25,000 units every 8 hours (Group I), a bolus dose on day one of *E. coli* C25 monoassociation (Group II); and a bolus dose on day 2 of *E. coli* C25 monoassociation (Group III).

† HBSS *versus* IL-2-treated mice by chi square analysis with a Yates continuity correction.

HBSS-Hanks balanced salt solution.

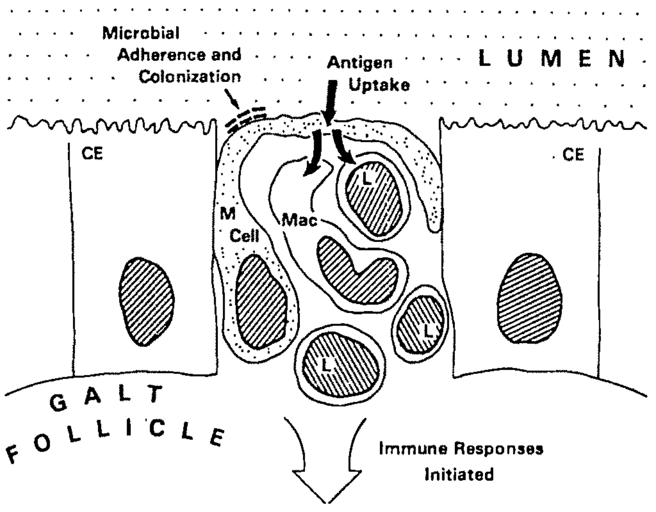

FIG. 3. Peyer's patch in the intestine. An M cell, the surface of which is in contact with the contents of the intestinal lumen, is surrounded by subepithelial macrophages (Mac) and by lymphocytes (L). M cells are important sites of antigen and microbe uptake by the GALT.

MLN, liver, and spleen in T cell-deficient nude mice was determined and was also found to be essentially zero. This, combined with the experiments utilizing CSA, anti-L3T4 antibody, and ATG, clearly demonstrates that suppression of T cell function or number has little effect on the ability of the GI tract to prevent translocation in animals in which gut microflora is unaltered and in which there is no other predisposition to translocate. It would appear then that in animals without other predisposing factors to translocate (such as bacterial overgrowth or disruption of epithelial integrity), T cell immunity is not of primary importance in the prevention of bacterial translocation.

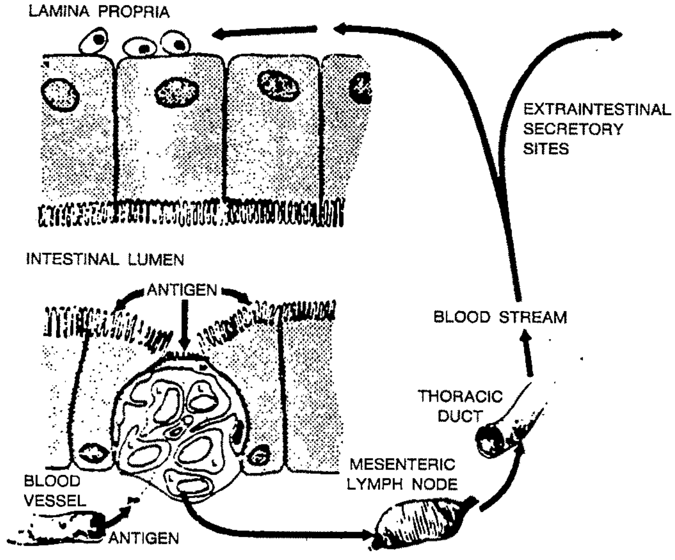

FIG. 4. Schematic representation of the induction of an immune response within the GALT. After antigen is processed by a Peyer's patch, antigen-specific T and B lymphoblasts enter the systemic circulation via the thoracic duct and then home to the lamina propria of the intestine. There they mature to antigen-specific T cells, B cells, and plasma cells, which are committed to the production of IgA for secretion into the intestinal lumen.

Under most of the experimental circumstances in which translocation occurs, it has been found that bacteria translocate most often to the MLN.[9] Only with severe insults to the intestine (ischemia or a combination of bacterial overgrowth and 20% body surface area burns)[20] will bacteria seed systemic sites such as the liver and spleen. Since, in the absence of direct intestinal damage, bacterial translocation is limited to the MLN, it appears that local factors within the MLN (for example T cell lymphokines) may exert a significant influence on the containment of bacteria that are translocating to the MLN.

To examine this question, a model of translocation was used which reliably induces translocation (in immunocompetent mice) of bacteria only to the MLN and rarely (<10%) to the liver or spleen. Monoassociation of (1) immunocompetent mice treated with 3 mg ATG/d for 6 days, (2) T cell-deficient nude mice with a conventional gut flora prior to monoassociation with *E. coli* C25, and (3) T cell-deficient nude germ-free mice with *E. coli* C25 yielded an equivalent incidence of translocation to the MLN. However, in all three experiments the MLN continued to be the site at which translocating *E. coli* C25 was contained since the spleen, liver, and peritoneum were invariably sterile. These results demonstrate that the MLN does, with this degree of translocation, serve as a point where translocating bacteria are entrapped and that T cells or their secreted factors play a small role in the prevention of systemic bacterial spread.

A rather striking and consistent trend noted in these experiments, however, was that suppression of T cell function did increase the average number of viable *E. coli* C25 per MLN. Although statistical significance was not achieved in the experiment in which germ-free nude mice were monoassociated, the trend was similar. The mechanism of this increase in bacteria per MLN is unknown. Whether due to an increased rate of translocation from the intestine or due to an impairment of the microbicidal environment of the lymph node, the results suggest that defects in T cell immunity may make the MLN a focus of persistent infection when there is translocation to it from whatever cause.

Finally, the influence of T cell stimulation on the translocation of *E. coli* C25 was investigated through the systemic administration of recombinant IL-2. IL-2 is a lymphokine produced by T-helper cells that stimulates the growth of activated lymphocytes *in vitro.* When administered *in vivo* IL-2 has a variety of effects including enhancement of T helper and T cytotoxic cell reactivity to antigens,[23] reversal of several T cell immunodeficiencies in nude mice,[24,25] and the generation of cells that have the ability to lyse tumors *in vitro.*[26]

We found that a total dose of 150,000 units significantly decreased the overall incidence of translocation of *E. coli* C25 to the MLN. To be effective, it was necessary to administer the 150,000 units in divided doses of 25,000 units every 8 hours during the 2-day period of oral monoassociation with *E. coli* C25. A single bolus dose of 150,000 units either on the first or second day of *E. coli* C25 monoassociation was ineffective at reducing translocation. Since during the 2 days of monoassociation with *E. coli* C25 there presumably is continuous translocation of *E. coli* C25 to the MLN, and since the serum activity of an intraperitoneal dose of IL-2 persists for approximately 2–3 hours,[27] it is not surprising that the single bolus dose of 150,000 units was ineffective in decreasing translocation. However, since the immediate effect of the single bolus dose of 150,000 units on translocation was not tested by culturing the MLN within hours after IL-2 administration, it is possible that a decrease in the translocation of *E. coli* C25 may have been missed.

What role the *in vivo* generation of LAK cells played in diminishing translocation of *E. coli* C25 to the MLN is unknown. Although the cellular origin of LAK cells is at present unresolved, it appears that a substantial number are formed from preexisting natural killer (NK) cells.[28] To date, no studies of any possible antimicrobial activity of LAK cells have been performed, but a recent report has shown that a subpopulation of NK cells does possess phagocytic and microbicidal capabilities for the gram-positive microbe *Staphylococcus aureus.*[29] However, these same NK cells were unable to phagocytose either *E. coli* or *Pseudomonas aeruginosa.* Whether treatment with IL-2 can either expand this population of NK cells or induce them to become phagocytic for gram-negative bacteria is speculative, but given the intense degree of proliferation of LAK cells within the MLN that occurs after systemic IL-2 administration,[26] this remains a possibility.

An alternative explanation is that IL-2 may have enhanced the specific immune response to *E. coli* C25 within the GALT. Given the brief 48-hour period of exposure to IL-2, it seems unlikely that an increased secretion of IgA specific for *E. coli* C25 into the gut lumen would have occurred. However, within the MLN antigen-specific lymphocytes already exposed to *E. coli* C25 may be more rapidly induced in the presence of IL-2, and, if combined with a general increase (induced by IL-2) in the release of macrophage activating lymphokines (such as gamma interferon), there could be an increased microbicidal capacity of macrophages within the lymph node leading to increased killing of *E. coli* C25. Relevant to this concept is the recent demonstration by Holter et al. that gamma interferon and lipopolysaccharide can induce IL-2 receptors on peripheral blood monocytes and that, if subsequently exposed to IL-2, the monocytes display increased H_2O_2 activity, suggesting an increase in their microbicidal activity.[30] Regardless of the specific mechanism, it is likely that the phenomenon of decreased translocation of *E. coli* C25 after treatment with IL-2 is due to a local process within the MLN and not within the intestine since *in vivo* administration of IL-2 has been shown to have little, if any, proliferative effect on lymphocytes within the intestine.[26]

In conclusion, T cell immunity appears to have little effect on the prevention of the movement of bacteria from the gut lumen to the MLN. However, by influencing either the antibody response to translocating bacteria or the local microbicidal activity of the MLN against translocating bacteria, normal T cell function does appear to have a modest impact on the ability of the GALT to effectively deal with translocating bacteria. In a critically ill surgical patient who is receiving systemic antibiotics (the majority of which have a marked impact on the composition of the intestinal flora), combined with ileus (with its attendant stasis of gut contents), malnutrition (with impaired ability of the gut epithelial cells to renew themselves), and shock or low flow states (with reduction in blood flow to the intestines), the function of the host's immune system, particularly T cell function within the lymph nodes draining the gut, may assume importance in the ability to control translocating gut bacteria.

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Further Evidence that Accelerated Muscle Protein Breakdown During Sepsis Is Not Mediated by Prostaglandin E_2

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Prostaglandin E_2 (PGE_2) reportedly increases protein breakdown in skeletal muscle. The role of PGE_2 for accelerated muscle proteolysis during sepsis, however, is controversial. In this study, the effect of the prostaglandin synthesis inhibitor indomethacin on PGE_2 release and protein breakdown in skeletal muscle from nonseptic and septic rats was evaluated. Sepsis was induced in male Sprague-Dawley rats (40–60 g) by cecal ligation and puncture (CLP). After 16 hours the extensor digitorum longus (EDL) and soleus (SOL) muscles were dissected with intact tendons and incubated in an oxygenated medium, and the release of tyrosine (protein breakdown) and PGE_2 into the incubation medium was determined. Paired muscles were incubated in the absence or presence of indomethacin (3 μmol/L or 6 μmol/L). In some experiments the effect of indomethacin was investigated in the presence of different concentrations of insulin (1, 10, or 100 mU/mL) since previous reports suggested an interaction between insulin and prostaglandins on protein turnover in skeletal muscle. In other experiments muscles were incubated in a flaccid or stretched state, which is known to influence the metabolic response to different substances. Protein breakdown rate was 0.210 ± 0.013 and 0.492 ± 0.025 μmol Tyr/g × 2 hours in EDL from nonseptic and septic rats, respectively ($p < 0.01$). The corresponding values for SOL were 0.480 ± 0.037 and 0.712 ± 0.039 μmol Tyr/g × 2 hours ($p < 0.01$). Addition of indomethacin to the incubation medium reduced PGE_2 release from 29.1 ± 3.1 to 6.8 ± 0.7 ng/g × 2 hours in nonseptic SOL and from 50.6 ± 10.4 to 5.6 ± 0.7 ng/g × 2 hours in septic SOL. Protein breakdown rate in SOL and EDL from sham-operated or septic rats was unaffected by indomethacin, both when muscles were incubated in a flaccid or stretched state, and when they were incubated in the presence or absence of insulin. The present results do not suggest a role of PGE_2 for accelerated muscle proteolysis in the present experimental septic model.

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THE ROLE of prostaglandin E_2 (PGE_2) for accelerated muscle proteolysis during trauma and sepsis is controversial, with various laboratories reporting differing results. Thus, while some authors reported data suggesting a link between PGE_2 synthesis and increased muscle protein breakdown,[1-3] other studies demonstrated that protein degradation remained elevated in postinjury skeletal muscle despite inhibition of prostaglandin synthesis by indomethacin.[4,5]

In a recent study from this laboratory, the accelerated protein breakdown in incubated soleus (SOL) muscles from septic rats was unaffected by indomethacin despite a 50% reduction in prostaglandin synthesis,[6] and it was suggested that increased muscle proteolysis during sepsis is not mediated by PGE_2.

Recent reports demonstrated an interaction between prostaglandins and insulin on different metabolic processes in skeletal muscle,[7,8] and indomethacin affected protein turnover in gastrocnemius and plantaris muscles of rats only in the presence of insulin.[8] Since in our previous report[6] muscles were incubated in a medium without insulin, it could be argued that the failure of indomethacin to reduce protein breakdown was due to the absence of insulin in the *in vitro* system. Other *in vitro* conditions may have rendered the muscles unresponsive to indomethacin as well, for example, the fact that the muscles were incubated in a flaccid rather than stretched state,[9] and that the effect of indomethacin *in vitro* was only tested in one type of skeletal muscle, namely, the red, slow SOL muscle. Regulation of protein turnover may differ in different types of skeletal muscle, and varying responsiveness to hormones and other substances has been reported in white, fast, and red, slow muscle, respectively.[10-12]

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TABLE 1. *Release of Tyrosine ($\mu mol \times gww^{-1} \times 2\ h^{-1}$) from SOL Muscles Incubated in the Presence of Different Concentrations of Insulin**

Insulin (mU/mL)	Indomethacin	Nonseptic Muscle	Septic Muscle
0	–	0.480 ± 0.037	0.712 ± 0.039
0	+	0.483 ± 0.042	0.720 ± 0.034
		NS	NS
1	–	0.374 ± 0.020	0.444 ± 0.012
1	+	0.400 ± 0.018	0.445 ± 0.019
		NS	NS
10	–	0.365 ± 0.048	0.458 ± 0.019
10	+	0.292 ± 0.023	0.453 ± 0.026
		NS	NS
100	–	0.496 ± 0.018	0.535 ± 0.022
100	+	0.504 ± 0.028	0.520 ± 0.022
		NS	NS

* Seven paired muscles were incubated in the absence or presence of indomethacin (3 μmol) at each insulin concentration.

The purpose of the present study was to further test the hypothesis that accelerated protein breakdown in skeletal muscle from septic animals can be regulated by the prostaglandin synthesis inhibitor indomethacin, with special emphasis on *in vitro* conditions that may affect the responsiveness in incubated muscles. A better understanding of the role of prostaglandins for increased muscle protein breakdown is important since the use of indomethacin or other cyclooxygenase inhibitors has been proposed in the treatment of postinjury and septic catabolism.[2,13,14]

Materials and Methods

Young male Sprague-Dawley rats weighing 40–60 g were used. Rats of this size possess thin extensor digitorum longus (EDL) and SOL muscles, which facilitates oxygenation of the tissue during incubation *in vitro.*[15] Septic muscles were harvested from rats 16 hours after cecal ligation and puncture (CLP), performed as described earlier.[6] Nonseptic muscles were dissected from rats 16 hours after sham operation, namely, laparotomy and manipulation of the cecum. Animals were resuscitated with saline (5 mL/100 g body weight, subcutaneously) at the time of operation and were thereafter fasted but allowed water *ad libitum.*

Protein Degradation

The EDL and SOL muscles were dissected with intact tendons under ether anesthesia, weighed, and preincubated for 30 minutes in 3 mL of a medium consisting of Krebs-Henseleit bicarbonate buffer (pH 7.4) supplemented with 5 mmol/L glucose. The incubation medium was saturated with 0_2:CO_2 (95:5), and incubation was performed at 37 C in a shaking water bath. After preincubation, muscles were transferred to 3 mL of fresh medium containing cycloheximide (0.5 mmol/L), and rate of protein degradation was determined by measuring the amount of tyrosine released into the medium.[16,17] Tyrosine was measured with high performance liquid chromatography. In some experiments the incubation medium was supplemented with a complete amino acid mixture (with the exception of tyrosine) at normal plasma concentration, 2% defatted bovine albumin, and 5 mmol/L glucose. Muscles were routinely incubated in a flaccid state. In other experiments they were mounted on small wire frames at approximate resting length. In studies using insulin or indomethacin, the substances were present in the medium both during preincubation and incubation. Indomethacin was dissolved in 50% ethanol before it was added *in vitro.* A corresponding volume of ethanol (10 μl/mL) was added to incubation flasks containing control muscles. Contralateral muscle from the same animal always served as control.

Prostaglandin E_2

PGE_2 production by incubated muscles was determined by radioimmunoassay of PGE_2 that was released into the medium, as described previously.[6]

Statistics

Results are given as mean ± SEM. Wilcoxon's nonparametric test for paired differences was used for statistical comparisons.

Results

When nonseptic or septic SOL muscles were incubated in the absence of insulin, addition of 3 μmol/L indomethacin to the incubation medium did not significantly affect protein degradation rate (Table 1), confirming a previous report from this laboratory.[6] The concentration of indomethacin used here effectively blocked PGE_2 production by incubated muscles in previous studies[1,6] and prevented the increase in protein degradation rate induced by arachidonic acid, added *in vitro.*[1] Also, when muscles were incubated in the presence of different insulin concentrations, ranging from 1 mU/mL to 100 mU/mL, indomethacin did not affect protein degradation rate (Table 1).

Although PGE_2 release from incubated muscles was effectively blocked by indomethacin at a concentration of 3 μmol/L,[1,6] we wanted to test whether this indomethacin concentration was too low to affect protein degradation. The concentration of the substance in the incubation medium was therefore increased to 6 μmol/L, but even then protein degradation was unaffected despite a marked reduction of PGE_2 release (Table 2). The PGE_2 release rates reported here are higher than in our previous study,[6] probably due to the fact that the experiments described in Table 2 were performed with

TABLE 2. *Release of Tyrosine (μmol × gww^{-1} × 2 h^{-1}) and PGE$_2$ (ng × gww^{-1} × 2 h^{-1}) from SOL Muscles Incubated in the Presence of 100 mU/mL of Insulin with or without 6 μmol/L Indomethacin*

	Tyrosine Release		PGE$_2$ Release	
Indomethacin	Nonseptic Muscle	Septic Muscle	Nonseptic Muscle	Septic Muscle
–	0.474 ± 0.032	0.655 ± 0.031	29.1 ± 3.1	50.6 ± 10.4
+	0.462 ± 0.025	0.685 ± 0.042	6.8 ± 0.7	5.6 ± 0.7
	NS	NS	$p < 0.02$	$p < 0.02$

Results are from seven paired nonseptic and septic muscles.

P values indicate significant *versus* muscles incubated without indomethacin.

insulin in the incubation medium. The almost doubled PGE$_2$ release in septic compared with nonseptic muscle is similar to our previous report.[6]

Thus, it is not likely that previous results[6] were due to the fact that insulin was not present in the incubation medium or that the concentration of indomethacin was too low. Another reason why indomethacin did not affect protein breakdown could be that the time during which the muscles were exposed to the substance was too short. Nonseptic and septic SOL muscles were therefore incubated for 6 hours in the absence or presence of 3 μmol/L indomethacin. A linear release of tyrosine from incubated rat SOL muscles for up to 6 hours was demonstrated previously.[18] Also during this extended incubation period, indomethacin did not affect protein breakdown rate, which was 0.998 ± 0.030 and 0.999 ± 0.032 μmol Tyr × gww^{-1} × 6 h^{-1} in seven paired nonseptic SOL muscles, incubated without or with indomethacin, respectively. The corresponding values for seven paired septic SOL muscles were 1.183 ± 0.119 and 1.100 ± 0.107 μmol Tyr × gww^{-1} × 6 h^{-1} (NS).

In previous reports, muscles were in a less catabolic state if incubated in a stretched, rather than flaccid, state.[9] Perhaps more important for this study, the response to different substances *in vitro* varied, depending on whether muscles were incubated in a stretched or flaccid state.[19–21] When nonseptic or septic SOL muscles were incubated stretched to resting length, protein breakdown remained unaffected by indomethacin (Table 3).

TABLE 3. *Release of Tyrosine (μmol × gww^{-1} × 2 h^{-1}) from SOL Muscles Incubated in a Stretched State*

	Indomethacin	Tyrosine Release
Nonseptic muscle (7)	–	0.328 ± 0.037
	+	0.304 ± 0.021
		NS
Septic muscle (7)	–	0.421 ± 0.053
	+	0.392 ± 0.053
		NS

Paired muscles were incubated in the absence or presence of indomethacin (3 μmol/L).

Numbers in parentheses indicate number of paired observations.

Most incubations in the present study and all incubations in our previous report[6] were performed with an unsupplemented medium. Since the response to various substances may be different if muscles are incubated under more physiologic conditions, experiments were performed in which muscles were incubated in the presence of an amino acid mixture and albumin. Results showed that protein breakdown rates were generally lower in this supplemented medium (Table 4 [compare with Table 1]). Also under these conditions, protein breakdown remained unaffected by indomethacin, both in nonseptic and septic muscle (Table 4).

Protein turnover rates are different in different types of skeletal muscle,[17] and the response to various conditions and substances may be different in the red, slow SOL muscle and the white, fast EDL muscle.[10–12] In the present study, we therefore also tested the effect of indomethacin on protein degradation in incubated EDL muscles from nonseptic and septic rats. Again, protein breakdown rate was not significantly altered by indomethacin (Table 5).

Discussion

The present study demonstrated that accelerated tyrosine release in incubated skeletal muscle from septic rats was not affected by indomethacin, despite the fact that PGE$_2$ production was markedly reduced. The results confirm a recent study from this laboratory,[6] and suggest that muscle protein breakdown in the present exper-

TABLE 4. *Release of Tyrosine (μmol × gww^{-1} × 2 h^{-1}) from SOL Muscles Incubated in a Medium Supplemented with Amino Acids and Albumin*

	Indomethacin	Tyrosine Release
Nonseptic muscle (7)	–	0.243 ± 0.037
	+	0.249 ± 0.032
		NS
Septic muscle (7)	–	0.348 ± 0.054
	+	0.372 ± 0.036
		NS

Paired muscles were incubated in the absence or presence of indomethacin (3 μmol/L).

Numbers in parentheses indicate number of paired observations.

TABLE 5. *Release of Tyrosine ($\mu mol \times gww^{-1} \times 2\ h^{-1}$) from EDL Muscles Incubated in the Absence or Presence of Indomethacin (3 μmol/L)*

	Indomethacin	Tyrosine Release
Nonseptic muscle (7)	−	0.210 ± 0.013
	+	0.196 ± 0.014
		NS
Septic muscle (7)	−	0.492 ± 0.025
	+	0.424 ± 0.030
		NS

Numbers in parentheses indicate number of paired observations.

imental model is not regulated by prostaglandins. In nonseptic muscle as well, protein degradation was unaffected by indomethacin, similar to previous reports in which basal degradative rates were not determined by prostaglandin levels in control muscles.[1]

In the present study, the effect of indomethacin *in vitro* on protein breakdown was tested in muscle incubated under different conditions known to influence the response to indomethacin and other substances. Protein breakdown was unaffected by indomethacin when muscles were incubated in the absence or presence of different concentrations of insulin and when they were incubated in a flaccid or stretched state. Incubation in different types of medium did not render protein breakdown sensitive to indomethacin, and the substance failed to reduce proteolysis both in the red SOL and the white EDL muscle. Although the present results strongly suggest that accelerated protein breakdown in septic muscle is not mediated by prostaglandins, an alternative interpretation may be that PGE_2 is important in the initiation of proteolysis but not in its maintenance. This is less likely, however, since pretreatment of rats *in vivo* with indomethacin 45 minutes before induction of sepsis[6] or 2 hours before burn injury[4] did not affect muscle protein breakdown despite significant inhibition of PGE_2 production. Proteolysis in normal muscle incubated in the presence of plasma from septic animals remained elevated despite the fact that indomethacin was present in the incubation medium from the start of incubation,[6] further suggesting that PGE_2 is not important for initiation or maintenance of proteolysis.

The concept of a role of PGE_2 for increased muscle proteolysis in trauma and sepsis originated from studies in which the addition of PGE_2 to incubated muscles stimulated protein breakdown.[1] In subsequent experiments, administration *in vitro* of leukocytic pyrogen enhanced PGE_2 production and protein degradation in incubated muscles, and both effects were abolished by indomethacin.[2] When indomethacin was administered to rats, urinary excretion of nitrogen decreased, and although the results were interpreted as indicating impaired renal function,[22] it is possible that the data reflected reduced protein breakdown as well. In other studies, muscle protein breakdown increased following intra-arterial infusion of PGE_2.[3] Thus, it is obvious that high levels of PGE_2 can induce muscle protein breakdown. However, there is no convincing evidence in the literature that muscle protein degradation is regulated by prostaglandins in any physiologic or pathologic condition despite the fact that prostaglandin synthesis was increased in various conditions characterized by accelerated muscle proteolysis.[5,6] On the contrary, several lines of evidence argue against a role of prostaglandins for the regulation of muscle proteolysis.

In addition to the present study and a recent report from this laboratory,[6] other investigators as well failed to reduce postinjury catabolism despite inhibition of prostaglandin synthesis. Administration of indomethacin to burn-injured rats did not affect the elevated protein breakdown rate in incubated epitrochlearis muscle despite the fact that PGE_2 release by the muscles was reduced from 22.1 to 8.5 ng/g × 2 h.[4] In the same study, indomethacin added *in vitro* (3 μmol/L) to incubated muscles from burned rats decreased PGE_2 release but did not affect the high rate of protein degradation. Similar results were observed in a more recent study in which proteolysis in incubated SOL muscles from rats following burn injury remained elevated in spite of 90% inhibition of PGE_2 production with aspirin or indomethacin.[5] In contrast to these studies, a recent report demonstrated inhibited muscle wasting and cathepsin B activity in EDL and SOL muscles from septic rats treated with indomethacin.[23] However, since no measurements of protein turnover rate or muscle protein content were made in that study, it is not known if protein degradation was affected by indomethacin. When the cyclooxygenase inhibitor ibuprofen was administered to healthy volunteers who were treated with endotoxin, fever and flu-like symptoms were reduced and the ACTH and cortisol release were blocked.[24] In contrast, the increased oxygen consumption and several other components of the acute phase response were unaffected by ibuprofen, suggesting that metabolic alterations during endotoxemia may persist despite effective blockade of prostaglandin synthesis.

Administration of insulin *in vivo*[8] or *in vitro*[25] increased prostaglandin synthesis and concentration in skeletal muscle tissue. From other studies it is well known that insulin reduces muscle protein breakdown.[10,26-28] Reduced muscle proteolysis in the presence of high concentrations of prostaglandins, including PGE_2, does not support the concept of a role of this substance as a mediator of increased muscle protein breakdown. In the present study, septic muscles were incubated in the presence of high concentrations of insulin, two factors that probably contributed to increased tissue levels of PGE_2. In spite of this, indomethacin did not affect protein degradation rate. It should be noted, however, that the stimulatory effect of insulin on protein synthesis is probably mediated by prostaglandins. Thus, muscle concentration of $PGF_{2\alpha}$, which is known to increase muscle protein synthesis in skeletal muscle,[1] was elevated by insulin, and the insulin-induced stimulation of protein synthesis was blocked by indomethacin.[8,25]

Incubation of skeletal muscle in a stretched rather than flaccid state resulted in increased protein synthesis and reduced protein degradation rate.[9,19] Intermittent stretching of isolated muscles increased protein synthesis and $PGF_{2\alpha}$.[21] Thus, incubated stretched muscles is another example of a condition in which muscle catabolism is reduced despite elevated levels of prostaglandins, further suggesting that PGE_2 is not an important mediator of accelerated muscle proteolysis.

Although the present results suggest that accelerated muscle proteolysis during sepsis is not induced by PGE_2, it should be emphasized that results were achieved in an experimental septic model using small rats and muscles incubated *in vitro.* The possible role of prostaglandins for increased muscle protein breakdown in septic patients remains to be determined. It should also be pointed out that protein degradation was measured as release of tyrosine from incubated muscles. Tyrosine release reflects total protein breakdown, and recent studies suggested that changes in myofibrillar protein breakdown, measured as release of 3-methylhistidine, can go undetected when tyrosine release is used to assess protein breakdown rate.[29] In future experiments, the effect of indomethacin on myofibrillar protein breakdown should be studied to further elucidate the role of prostaglandins for regulation of muscle protein breakdown during sepsis.

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Long-term Follow-up of Patients with Biopsy-proven Benign Breast Disease

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Three hundred sixty-five patients with biopsy-proven benign breast disease were followed annually in a prospective manner for 4–15 years to analyze breast cancer development, recurrence, and efficacy of management during follow-up. Eleven breast cancers developed in 11 patients during follow-up, giving a 2.6-fold increased cancer risk over the reference population. No association was found between patients who developed cancer and those who did not with respect to the initial histologic feature ($p = 0.62$), the age at entry by decades ($p = 0.40$), and relative to menopause ($p = 0.54$), the presence of cysts ($p = 0.87$), or calcification ($p = 0.74$) in the biopsy specimen, a family history of breast cancer ($p = 0.80$), or the number of observation years ($p = 0.27$). We conclude that an aggressive approach to benign breast disease is not justified for any type of lesion as defined in this report. Benign breast disease does not inevitably lead to recurrence. Moreover, 41% of our patients never had any recurrence and were free of symptoms during follow-up; 67% never had a mammogram and 82% never required a further operation. There was no association with initial histologic feature in patients who had clinical examination only and those who had mammogram, biopsy, or both during follow-up ($p = 0.93$). Mammograms were mainly used to clarify a clinical recurrence than as a screening tool, regardless of histologic feature ($p = 0.76$). Mammograms were mainly used in premenopausal patients ($p < 0.001$) having lumps ($p < 0.001$), namely, the most difficult patients for radiologic interpretation. This may be one important reason for the rather low sensitivity (75%) and specificity (40%) of mammography in this report. In conclusion, clinical examination is the outstanding investigational tool to follow patients with biopsy-proven benign breast disease, especially in young premenopausal patients.

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THE DIFFICULTY in understanding benign breast disease is reflected in the large spectrum of recommendations for its further management; benign breast disease remains a vexing clinical problem. While special concern always arises with its role in breast cancer development, little is known about recurrence and preferential pattern of management in practice of patients with benign breast disease. In this report the data of a prospective long-term follow-up of patients with biopsy-proven benign breast disease are analyzed with respect to cancer development and recurrence, as well as the pattern and efficacy of further management.

Materials and Methods

All women operated for benign breast disease in our clinic since January 1, 1970 are followed up annually in a prospective manner. Patients operated for the initial lesion between 1970 and 1981 inclusive are the subjects of this report. Each patient has been examined annually by the same two clinicians, followed by mammograms, biopsies, or both when deemed appropriate. In addition to these formal assessments, the patient may be referred by family doctors for mammograms, biopsies, or both because of breast problems. All investigations were taken into account in this study.

All slides of initial and subsequent lesions were reinterpreted and classified in a uniform manner by two pathologists by blind duplicate readings without the knowledge of subsequent breast cancer development (Table 1). Throughout this paper we use the term breast cancer to mean invasive breast cancer. A benign biopsy specimen is defined as one that contained neither invasive breast cancer nor a carcinoma in situ. Patients with a previous history of breast cancer were excluded from the study, but breast cancer development during follow-up was no reason for exclusion. Bilateral simultaneous biopsies are counted as one operation, the lesion with the more distinct alteration being considered for classifi-

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TABLE 1. *Classification of Histologic Type of Lesion*

1	Fibrocystic disease without proliferation and atypical hyperplasia, consistent with mastopathia cystica fibrosa I of Prechtel[21] and with the A II-lesion of Wellings et al.[22]
2	Proliferative disease without atypical hyperplasia, consistent with mastopathia cystica fibrosa II of Prechtel,[21] with "epitheliosis" of Azzopardi,[23] with the A III-lesion of Wellings et al.,[22] and with ductal hyperplasia of the WHO classification.
3	Proliferative disease with atypical hyperplasia, consistent with mastopathia cystica fibrosa III of Prechtel[21] and with atypical ductal and lobular hyperplasia of the WHO classification.
4	Lipomatosis and fibrosis.
5	Adenosis and fibrosing adenosis.
6	Fibroadenoma.
7	Remainder regressive changes (inflammation, liponecrosis, lipogranuloma, hematoma).

TABLE 2. *Classification of Original Mammographic Test Results*

1	Definitely benign.
2	Probably benign (not optimal radiologic presentation); repeat mammogram indicated.
3	Probably malignant (one radiologic feature of malignancy); early repeat mammogram or biopsy indicated.
4	Definitely malignant; biopsy strongly advised.

cation. The initial lesion was bilateral in 36 patients. All biopsies were performed under supervision in a resident teaching program. Fine-needle aspiration cytology was not used. The originally reported interpretations of the mammograms performed during follow-up were classified according to their test result (Table 2).

The data were analyzed using the SPSS PC statistical package on an IBM-XT computer. Chi square contingency analyses, the Fisher's exact test, one-way ANOVA, and median tests were used where appropriate. Statistical significance was accepted at a $p < 0.05$.

Follow-up

Between 1970 and 1981 inclusive, 383 women (100%) were operated for benign breast disease and therefore qualified for the study. Eighteen patients were lost and 365 (95%) were followed up to 15 years with a total of 3145 observation years and a mean follow-up time of 8.6 years. Three hundred thirty-seven patients (88%) had a complete follow-up until 1985 with a minimal follow-up time of 4 years, while 28 patients had an incomplete one: two due to death from breast cancer, 11 due to death of unrelated causes, 12 due to departure, and three due to lack of cooperation.

Results

Pattern of Age at Entry, Initial Histologic Feature, and Family History of Breast Cancer

The distribution of the 365 patients according to the age at entry by decades and initial histologic feature is shown in Table 3. The mean age at entry of the 365 patients was 42.6 years. The follow-up periods for each decade did not differ markedly except for those patients older than 70 years of age where the follow-up time was somewhat shorter. In 65 patients, the initial lesion was proliferative without atypia and in 28 patients proliferative with atypia. The follow-up periods for the cohorts according to type of initial lesion did not differ markedly except for patients with fibrocystic disease without proliferation and for patients with regressive changes where the follow-up time was somewhat longer.

A disproportional distribution of the 365 patients appeared if type of initial lesion was matched by age at entry. The median age of patients with fibroadenoma, adenosis and fibrosis, lipomatosis and fibrosis, and fibrocystic disease without proliferation was less than 43 years, whereas for patients with proliferative disease without and with atypia and regressive changes the median age was more than 43 years ($p = 0.016$). The presence of cysts of 0.3 cm in diameter or more was noted in 73 and the presence of calcification in 66 initial biopsy specimens; 23 of the 365 women had a family history of breast cancer in a mother or sister.

Breast Cancer Development

Eleven invasive breast cancers subsequently developed in 11 of 365 patients during follow-up, the overall annual cancer incidence being 3.5 per 1000 observation years. Using the data of the tumor registration office in Basel, Switzerland (unpublished), we determined the number of cases of cancer that would have been expected to occur in our studied population according to our observation period and to the age-specific distribution of our population. The ratio of our observed incidence to the predicted number is used to define the relative risk of 2.6 according to Kodlin et al.[1] We com-

TABLE 3. *Distribution of the 365 Patients According to Age at Entry and Type of Initial Lesion with Mean Follow-up Times*

Age at Entry (yr)	No. of Patients	Average Follow-up Time (yr)	Type of Lesion	No. of Patients	Average Follow-up Time (yr)
10–19	13	8.7	1	117	9.7
20–29	51	8.7	2	65	8.8
30–39	86	8.3	3	28	8.1
40–49	131	9.1	4	64	7.1
50–59	49	8.4	5	38	8.2
60–69	27	8.1	6	37	8.0
>70	8	5.8	7	16	9.6

TABLE 4. *Correlations with Breast Cancer Development*

	P Value
Age at entry by decades	0.39
Age at entry: premenopausal/perimenopausal/ postmenopausal*	0.54
Histologic type of initial lesion	0.62
Presence of calcification in the biopsy specimen	0.74
Presence of cysts in the biopsy specimen	0.87
Family history of breast cancer	0.80
No. of observation years (1–15 years)	0.27
No. of assessments	0.17
Presence of pain at assessment	0.28
Presence of lump at assessment	<0.001

* Premenopausal, <45 years; perimenopausal, 45–55 years; postmenopausal, >55 years.

pared the characteristics of those patients in our study who developed breast cancer during follow-up with those who did not (Table 4). When the patients are classified with respect to the age at entry by decades or relative to menopause, there was no significant difference between patients with cancer development and those without.

Furthermore, there was no significant association in the type of initial lesion in patients who developed cancer and those who did not. Patients with proliferative disease, with or without atypia, showed no significant difference in cancer incidence as compared to the rest of our study population. There was no correlation between cancer development and the presence of cysts or calcification in the initial biopsy specimen. In addition, there was no association between cancer development and a family history of breast cancer; moreover, not a single patient with cancer development during follow-up had a family history of breast cancer.

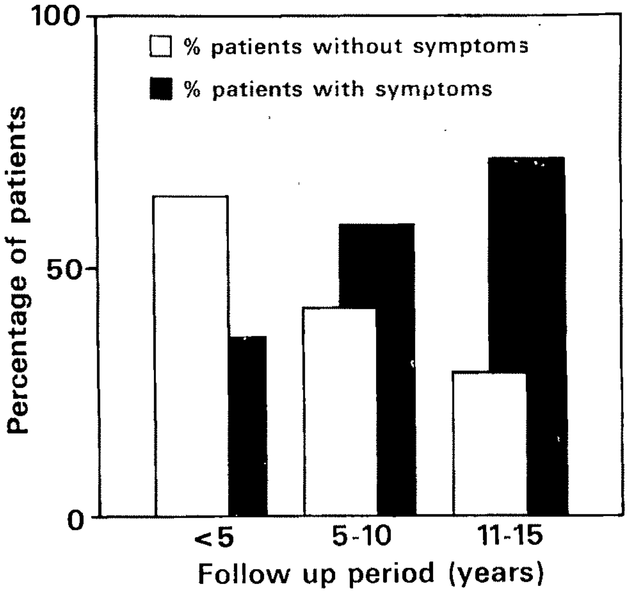

FIG. 1. Percentage distribution of patients with and without recurrence (pain and/or lump) at assessment, according to follow-up time (N = 365).

Patients with breast cancer development and those without had similar periods of follow-up. No association was found between presence of pain at control and breast cancer development, whereas the presence of lump at control was significantly associated with cancer development. All patients with cancer had a lump at control.

Recurrence

Lump and/or pain at assessment during follow-up was considered as recurrence. Figures 1 and 2 show the patterns of recurrence, cancer development, and performed investigations (mammograms and biopsies) during follow-up. The average age at entry was similar for each follow-up period related cohort ($p = 0.67$). With increasing follow-up time there was a significant increase of patients with recurrence ($p < 0.001$) and with subsequent investigations but no significant increase of patients with cancer development. However, of the 365 patients, 150 (41%) never had any recurrence at examination and were free of symptoms during follow-up, 300 (82%) never had a further operation, and 243 (67%) never had a mammogram.

Is recurrence confined to initial side and histologic feature? In 65 patients a reoperation was performed to clarify a recurrence during follow-up. There was no significant association between the side of reoperation and the side of the initial lesion ($p = 0.13$). However, there was an association between type of initial and subsequent lesion. In a significant number of patients the subsequent histologic feature was the same as the initial one ($p < 0.001$).

Is the clinical feature of the recurrence related to type of initial lesion or age at entry? Patients with a lump at assessment were younger (premenopausal) at entry than those without ($p < 0.001$). More patients with fibrocystic disease or proliferative disease without atypical hyperplasia as initial lesions had pain at assessment than would have been expected ($p < 0.001$). There was no association between lump at assessment and initial histologic feature ($p = 0.79$) and no association between pain at assessment and age at entry ($p = 0.15$).

Pattern of Management

Table 5 shows the distribution of the 365 patients according to type of initial lesion and subsequent management during follow-up. There was no significant association with initial histologic feature in patients who had clinical examination only during follow-up and those who had mammogram or biopsy or both during follow-up (p = 0.93).

Clinical examination. Two hundred twenty-three patients (61%) had regular clinical examinations only, at formal assessment and by family doctors, without mammogram or biopsy. A total of 11 breast cancers developed during follow-up in the 365 patients. Eight of them were detected by clinical examination only and three were predicted by mammograms. There was no difference in tumor size and lymph node involvement between the cancers detected by clinical examination only and those predicted by mammograms.

Mammogram. One hundred twenty-two patients (33%) had a total of 180 mammograms during follow-up; 19 mammograms were followed within 3 months by a biopsy and were used to determine specificity (40%) and sensitivity (75%) of mammography because of confirmed disease status. There was no significant difference between patients who had mammograms during follow-up and those who had not according to initial (p = 0.71) and subsequent (p = 0.52) histologic feature, number of controls (p = 0.30), and presence of pain at control (p = 0.07). A significant difference was found, however, according to age at entry and presence of lumps at control. Patients with mammograms were younger (less than 45 years) at entry (p = 0.001) and had more lumps at control (p < 0.001) than those without mammograms.

Biopsy. Sixty-five patients (18%) had one or more, ten had two or more, and three had three reoperations during follow-up. The more reoperations performed, the higher the ratio of detected cancers, 11% at the first, 20% at the second, and 67% at the third reoperation.

Discussion

Our patients with biopsy-proven benign breast disease had a 2.6-fold increased risk of breast cancer development as compared to the reference population, taking the age-specific distribution and period of follow-up into account. There is good agreement that patients with biopsy-proven benign breast disease are at increased cancer risk; estimates of the relative risk, however, have ranged from 1.4 to 4.8.[1-6] It is difficult to compare the different studies of benign breast disease, especially if the general population is used as a reference. The incidence of benign breast disease in the general population is not known,[7] and reliable information concerning other important breast cancer risk factors is absent. The slightly increased cancer risk in women with biopsy-proven benign breast disease may be the result of a disproportionate distribution of such factors rather than the result of benign breast disease *per se.* Therefore, we compared those patients in our study who developed breast cancer during long-term follow-up with those who did not. In contrast to other reports,[1-3,8] we found no association between type of initial histologic feature and cancer development; patients with atypical hyperplasia did not

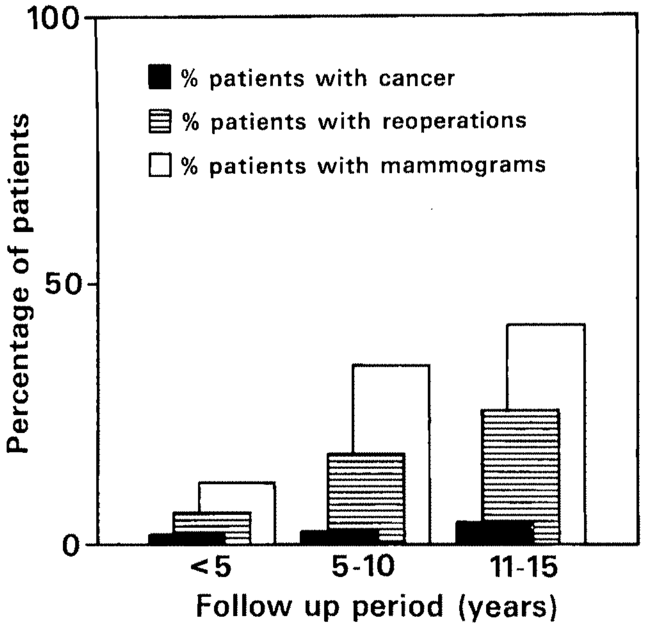

FIG. 2. Percentage distribution of patients with breast cancer development, mammograms, and reoperations, according to follow-up time.

TABLE 5. *Distribution of the 365 Patients According to initial Histologic Feature and Subsequent Management During Follow-up (Clinical Examination Only, Clinical Examination with Mammogram or Biopsy, or Both)*

	Examination		Mammogram		Biopsy		Mammogram and Biopsy		Total	
Histology	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
1	70	(60)	20	(17)	8	(7)	19	(16)	117	(100)
2	36	(55)	16	(25)	3	(5)	10	(15)	65	(100)
3	19	(68)	4	(14)	0		5	(18)	28	(100)
4	40	(63)	18	(28)	3	(5)	3	(5)	64	(100)
5	24	(63)	13	(34)	0		1	(3)	38	(100)
6	24	(65)	4	(11)	3	(8)	6	(16)	37	(100)
7	10	(63)	2	(13)	3	(19)	1	(6)	16	(100)

develop more cancers than patients with other histologic features. Caution in the interpretation of the data is indicated because of the limited number of patients with atypical hyperplasia in our study. However, it was pointed out that most of the histologic features do not place the patients at a markedly increased cancer risk, except the very small number of lesions similar to or consistent with carcinoma in situ.[2] Patients with carcinoma in situ as initial lesion were excluded from this study, and carcinoma in situ was not observed as recurrent lesion during follow-up.

Another surprising finding was the lack of association between age at entry and subsequent cancer development. Older patients at entry did not develop more cancers during follow-up than younger patients. Previous reports have shown similar correlations,[2] but caution in the interpretation is indicated because of the somewhat shorter follow-up of patients older than 70 years of age. There was no association between cancer development and the presence of cysts or calcification in the initial biopsy specimen. Patients with a family history of breast cancer did not develop more breast cancers during follow-up than those without. Dupont and Page[2] demonstrated that the presence of cysts or calcification or a family history of breast cancer alone had little effect on cancer development; patients with calcification in the biopsy specimen and a family history of breast cancer had a marked increased cancer risk only in conjunction with the rare lesions similar or consistent with carcinoma in situ. Patients with cysts and a family history of breast cancer were at increased cancer risk in their report,[2] but the two groups were not stratified according to histologic feature.

Biopsy-proven benign breast disease does not inevitably lead to recurrence with increasing follow-up time. Of the 365 patients with a follow-up time up to 15 years, 41% never had any recurrence at assessment and were free of symptoms, 67% never had a mammogram, and 82% never had a further operation. With increasing time of follow-up there was no increase in developing cancer, although there was an increase in recurrences (defined as pain or lump) and subsequent investigations. Patients counted as having recurrence during follow-up may have had these symptoms only once and may have been subsequently free of symptoms for the rest of the observation time. Thus, the recurrence rate may actually be overestimated in this report.

If a reoperation was necessary to clarify the recurrence, there was no association between the side of initial and recurrent lesion, but in a significant number of patients the subsequent histologic feature was the same as the initial one. About 60% of all patients followed for a period up to 15 years had clinical examination only, at formal assessment and by family doctors, without mammograms and/or biopsies; 33% of all patients had one or more mammograms in addition to clinical examination, and 18% one or more biopsies. There was no association with initial histologic feature in patients who had clinical examination only and those who had mammogram or biopsy or both during follow-up. The majority of cancers were detected by clinical examination only, and no difference was found in tumor size and lymph node involvement between the cancers detected by clinical examination only and those predicted by mammograms. These findings suggest that regardless of initial histologic feature, most patients were followed routinely by clinical examination only in daily practice in our district. Mammograms or biopsies were rather used to clarify a distinct recurrence than as a screening tool despite the clear recommendation to perform mammograms in patients with proliferative disease at annual intervals during follow-up.[8,9] The specificity of mammograms with confirmed disease status was 40% and the sensitivity 75%. The efficacy of mammography must be rated higher because mammograms with negative test results impeded biopsies in patients with recurrence but without cancer development during follow-up. However, in numerous studies sensitivity has ranged from 31% to 91% and specificity from 51% to 98%.[10-20] It was pointed out that the clinical and radiologic heterogeneity of the female breast is an important source of this wide range in reported efficacy of mammography. Breasts of premenopausal women and those with fibrocystic disease are more difficult to interpret roentgenographically than breasts of older subjects and those without fibrocystic disease.[10] The patients in our study having mammograms during follow-up were younger and had more lumps than patients without mammograms. Thus, in our study mammograms were used in the most difficult patient group for radiologic interpretation. This may well adversely influence the accuracy of mammography and may challenge this method as the method of choice to clarify recurrence in young patients with benign breast disease.

We conclude that an aggressive approach to biopsy-proven benign breast disease is not justified for any type of benign lesion as defined in this report. Clinical examination is the outstanding investigational tool to follow patients with biopsy-proven benign breast disease. The status of mammography in the follow-up of patients with benign breast disease is open to question, especially in young premenopausal patients.

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Further Evidence Supporting a Cause and Effect Relationship Between Blood Transfusion and Earlier Cancer Recurrence

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Studies of associations between perioperative blood transfusions and later recurrence of solid tumors have yielded conflicting results. A previous analysis of transfused patients suggested that recurrence was associated with transfusion of whole blood as opposed to red blood cell concentrates. Additional analyses were performed on patients with cancers of the colon, rectum, cervix, and prostate to determine if patients receiving whole blood, red blood cells only, or no transfusions had differing outcomes. Patients receiving 1 unit or more of whole blood had uniformly poor outcomes compared with nontransfused patients ($p < 0.001$). In contrast, patients receiving only red blood cells had progressively worse recurrence and death rates with increasing numbers of transfusions, suggesting the presence of a dose-effect relationship. Employing multivariate techniques, blood transfusions of ≤3 units that included any whole blood were independently and significantly associated with earlier recurrence ($p = 0.003$) and death due to cancer ($p = 0.02$). Transfusions of ≤3 units of blood comprised solely of red blood cell concentrates were associated with no greater risk of recurrence than that seen in patients receiving no transfusions ($p = 0.50$). These results provide a potential explanation for the disparate results reported in studies of blood transfusion and cancer outcome. The marked difference in outcome seen between patients receiving a few units of red blood cells and comparable patients receiving even one unit of whole blood are consistent with the hypothesis that transfusion of stored blood plasma causes earlier tumor recurrence in some instances. Strategies for reducing these risks might include avoidance of whole blood transfusions when only 1–3 units are required, more conservative transfusion practice, use of autologous blood transfusions, and perhaps, use of red blood cells washed free of plasma and white cell debris. Clinical trials to test these hypotheses are urgently needed.

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SINCE THE FIRST REPORT by Burrows and Tartter[1] numerous studies have appeared demonstrating a relationship between perioperative blood transfusions and later recurrence of solid tumors, including cancers of the colon and rectum,[2-6] lung,[7,8] breast,[9,10] kidney,[11,12] vulva,[13] cervix,[14] stomach,[15] and soft-tissue sarcomas.[16] An almost equal number of studies have found smaller or no differences between transfused and nontransfused patients.[17-26]

We recently reported that in patients with colorectal, cervical, or prostate cancers transfused with whole blood there was an independent association between transfusion and poorer clinical outcome.[27] Patients receiving small numbers (≤3) of red blood cell concentrates had fewer and later recurrences than patients receiving equivalent numbers of blood transfusions that included even 1 unit of whole blood. Patients receiving four or more red blood cell transfusions had recurrence and survival experiences similar to those of patients receiving whole blood transfusions. These differences could not be readily explained in terms of other prognostic factors such as age, type of tumor, clinical or histologic stage, preoperative anemia, length of follow-up, or duration of surgery (this last factor being employed as a surrogate measure of surgical difficulty).

These results led us to hypothesize that previous studies failing to find associations between blood transfusions and cancer recurrence might be explained in part by differing patterns of blood component usage. That is, if only red cell concentrates were transfused, and in small numbers, no or smaller differences in recurrence rates between transfused and nontransfused patients might be expected. We report here additional analyses of our previously reported patients intended to test this hypothesis. Comparison is made between the outcome

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in patients receiving no transfusions and that in patients receiving either small numbers of red blood cell concentrates only, or small numbers of transfusions that included at least 1 unit of whole blood. We also present data suggesting a dose-effect relationship between number of red cell transfusions and the likelihood of tumor recurrence.

Patients and Methods

The 216 transfused patients with cancer of the colon, rectum, cervix, or prostate have been previously reported as part of a comparison of cancer recurrence and death after whole blood or red cell transfusions.[27] Data on the nontransfused patients reported here for the first time were collected simultaneously as part of the same retrospective medical record review. Details of both clinical and statistical methods are identical for both this report and the previous study comparing red cell and whole blood recipients.[27] In brief, the names and identifying numbers of hospital patients seen between 1970 and 1982 with these diagnoses were retrieved from a computerized data base and the medical record reviewed, collecting a variety of demographic, clinical, and treatment data. Transfusion data were also confirmed from blood bank records. Patients were included in the study if they had undergone surgery at our institution, documented follow-up of at least 6 months was available, no evidence existed of metastatic disease at diagnosis, and the transfusion history and diagnosis of cancer were unambiguous. We designated patients as transfused if the transfusions occurred within a 1-month span before or after surgery. The vast majority of transfusions occurred immediately preoperatively, intraoperatively, or within a few days postoperatively. Patients receiving transfusions at other times are not included in this analysis. Individual multivariate analyses for each tumor, including proportional hazards risk models, have been published for the colon and rectal cancer data,[2,3] described in abstract for the cervical cancer data,[14] and are in press for the prostate cancer data. The results for each tumor analyzed separately suggested that transfusion is significantly associated with cancer recurrence and/or death due to the tumor, even after adjustment for clinical stage, anemia at diagnosis, duration of surgery, patient age, *etc.*

All transfused patients received either red blood cells, whole blood, or some combination of these components. A very small number of patients received fresh frozen plasma (13 of 216) or platelet concentrate transfusions (1 of 216). As initial analysis of the data suggested that recurrence was associated with transfusion of whole blood, we grouped the patients into those who had received only red cells and those receiving at least 1 unit of whole blood. Patients who received only red cells and fresh frozen plasma and/or platelets but no whole blood were grouped with the patients receiving whole blood.

A total of 216 transfused patients are analyzed of whom 120 had colon or rectal cancer, 62 had cervical cancer, and 34 had prostate cancer. The 354 nontransfused patients comprised 68 with colon or rectal cancer, 61 with cervical cancer, and 225 with prostate cancer. The numbers of recurrences and cancer related deaths for the colon/rectal, cervical and prostate groups were, respectively, (54; 20), (16; 8), and (19; 6) for the transfused patients and (6; 3), (18; 5), and (69; 21) for the nontransfused patients. The proportion of transfused patients having recurrences or death due to cancer was significantly higher than in the nontransfused patients for the colon/rectal and prostate cancer patients but not for those with cervical cancer. The trends for recurrence and death reported by kind and amount of blood transfused were similar for each tumor. A breakdown of the data by tumor is available from the authors.

Statistical Analysis

The methods detailed in our previous reports were employed.[3,27–31] The prognostic factors in our analyses included age, year of surgery, duration of surgery, admission hematocrit, kind and amount of blood components received, type of cancer, and stage of cancer. In order to analyze this last factor for patients with different types of cancer, an improvised classification was devised for statistical analysis purposes. Early stage included patients with cervical cancers of clinical Stages O and IA, colon and rectal cancers of histologic Stage A, and prostate cancers of clinical Stages A_1 and A_2. Intermediate stage included patients with cervical cancer Stages of IB, IIA, and IIB, colon, rectal, and prostate cancer Stages B_1 and B_2. Advanced stage included patients with cervical cancer Stages IIIA and IIIB, colon and rectal cancer Stages C_1 and C_2, and prostate cancer Stage C. We appreciated that this process would not yield precise data on the effect of Stage upon cancer recurrence, but wished to incorporate broadly representative information on stage in our study of prognostic factors that might be associated with transfusion and cancer recurrence.

When fitting proportional hazards models to time to recurrence and survival time, we first included as predictors all the previously noted prognostic factors, but not the type of blood component transfused.[30] The nonsignificant factors were excluded, and type of blood transfused (none, whole blood, red cells) was then added to the proportional hazards model to see if the change in the log-likelihood after adding transfusion status was

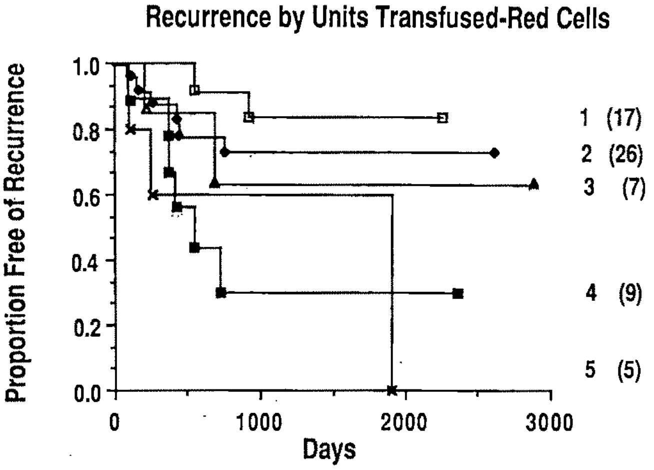

FIG. 1. The Kaplan-Meier plots for the estimated time to recurrence for patients receiving only red blood cell concentrates are shown. The numbers to the right of each line represent the number of units of red blood cells received by the patients in that group. The numbers in parentheses are the number of patients in that group. Six patients received more than five red blood cell units and had similar recurrence-free survivals to those receiving 4 or 5 units of red blood cells. These data are not shown. Because of the small number of patients in each group, data were pooled for statistical analysis. Patients receiving 1 or 2 units of red blood cells had significantly lower recurrence rates than those receiving 3 or 4 units (p = 0.02 by Breslow, 0.01 by Mantel-Cox). Patients receiving 2 or 3 units of red blood cells had significantly lower recurrence rates than those receiving 4 or 5 units (p = 0.06, 0.03). Patients receiving 3 or 4 units of red blood cells had similar recurrence estimates to those receiving 5 or more units (p = 0.98, 0.95).

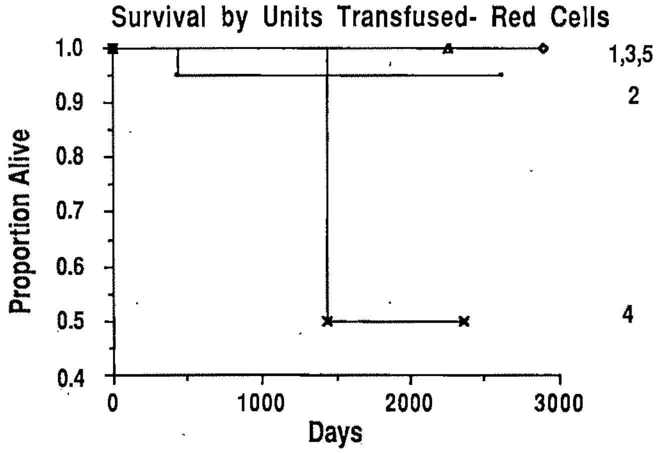

FIG. 3. The Kaplan-Meier plots for the estimated survival time for patients receiving only red blood cell concentrates are shown. The numbers to the right of each line represent the number of units of red blood cells received by the patients in that group. The numbers of patients in each group are identical to those in Figure 1. These curves are not significantly different from each other since there were only four deaths in these groups. However, when the six patients receiving >5 units of red blood cells are included in the analysis and data are pooled, patients receiving 1 or 2 units of red cells had significantly longer estimated survival times than those receiving 5 or more red blood cell transfusions (p = 0.03, 0.01).

significant. By entering information on transfusion last we could measure the impact of type of blood component transfused on time to recurrence and survival time after adjustment for other factors. We thus obtained an estimate of the effect on recurrence and death attributable to type of blood transfusion.

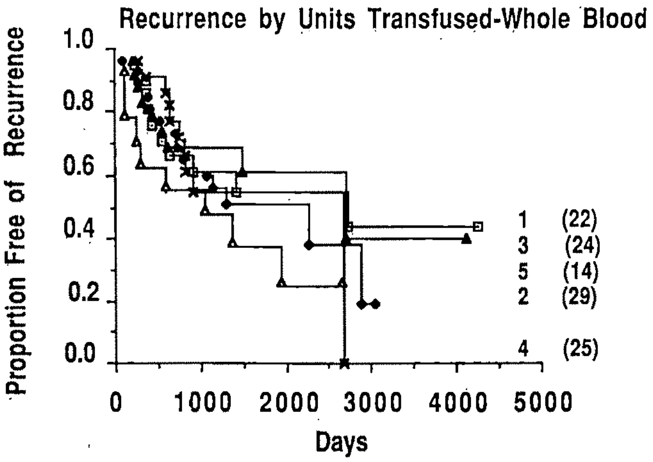

FIG. 2. The Kaplan-Meier plots for the estimated time to recurrence for patients receiving at least 1 unit of whole blood are shown. The numbers to the right of each line represent the total number of units of whole blood and red blood cells received by the patients in that group. The numbers in parentheses are the number of patients in that group. Thirty-two patients received a total of more than 5 whole blood and red blood cell units and had similar recurrence-free survivals to those receiving 1–5 units of whole blood and red cells. These latter data are not shown. None of the differences between these curves achieved statistical significance by the Breslow or Mantel-Cox tests (p = 0.46, 0.48 for the comparison of all the plots taken together).

Kaplan-Meier's product-limit method was used to estimate the unadjusted distributions of time to recurrence and survival time.[31]

Results

In our initial study of the transfused patients, earlier recurrence and death due to cancer was associated most strongly with any transfusion that included at least 1 unit of whole blood, and with transfusion of ≥4 units of red blood cells.[27] Therefore, we initially analyzed the unadjusted time to recurrence and survival time according to number of units of blood transfused by the Kaplan-Meier method. Estimates of the recurrence-free interval and survival time for patients receiving different amounts of whole blood or red blood cells are shown in Figures 1–4. The plots for the whole blood recipients are not statistically significantly different from each other (Figs. 2 and 4). The recurrence plots for the patients receiving only red blood cell transfusions are significantly different and suggest a dose-effect relationship (Fig. 1). That is, increasing numbers of transfusions appear to be associated with proportionally greater numbers of earlier recurrences. Because of the small number of deaths in the patients receiving only red blood cells, no assessment of a dose-effect relationship between number of transfusions and earlier death can be made in this group (Fig. 3).

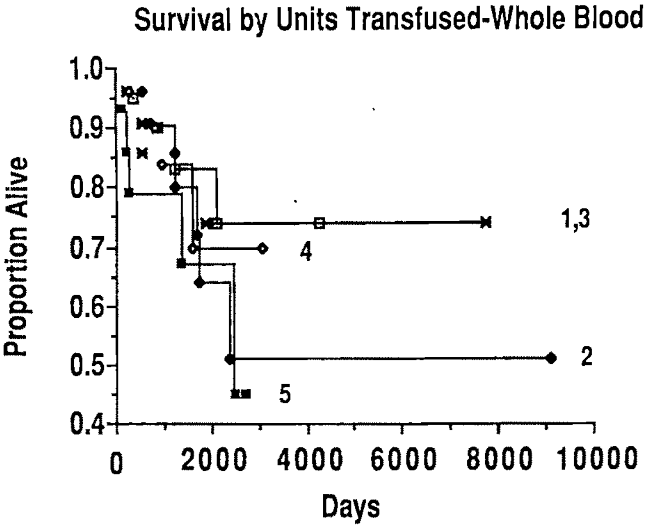

FIG. 4. The Kaplan-Meier plots for the estimated survival time for patients receiving at least 1 unit of whole blood are shown. The numbers to the right of each line represent the total number of units of whole blood and red blood cells received by each of the patients in that group. The numbers of patients in each group are identical to those in Figure 2. These plots are not statistically significantly different from each other (p = 0.52, 0.63). Addition of the patients receiving more than five transfusions and pooling of data do not alter the results of the analysis.

To assess the differences in recurrence and survival between patients transfused with comparable, small numbers of whole bloods or red blood cells, and those who were not transfused at all, we performed further Kaplan-Meier analyses on patients receiving no blood or no more than 3 units of blood. We limited this particular analysis to patients with mild to moderate blood loss in order to avoid including patients with particularly difficult resections or massive hemorrhages.

We further performed on this subset of our patients a multivariate proportional hazards risk analysis (Cox regression) of the factors predicting recurrence and death due to cancer, including patient age, year of surgery, duration of surgery, hematocrit on admission, type of cancer, histologic or clinical stage of cancer, and kind of blood component received. Because such a small proportion of the prostate cancer patients were transfused (13%) as compared with patients with colorectal (64%) or cervical (50%) cancer, the comparisons of pooled data between transfused and nontransfused patients were restricted to patients with colon, rectal, and cervical cancers. Only five patients with prostate cancer received red cells exclusively, an inadequate number for comparing the patients in this group with the 225 nontransfused patients. The 29 patients with prostate cancer who received whole blood transfusions or ≥4 units of red blood cells had significantly shorter recurrence-free intervals and survival times than the 225 nontransfused patients (data not shown).

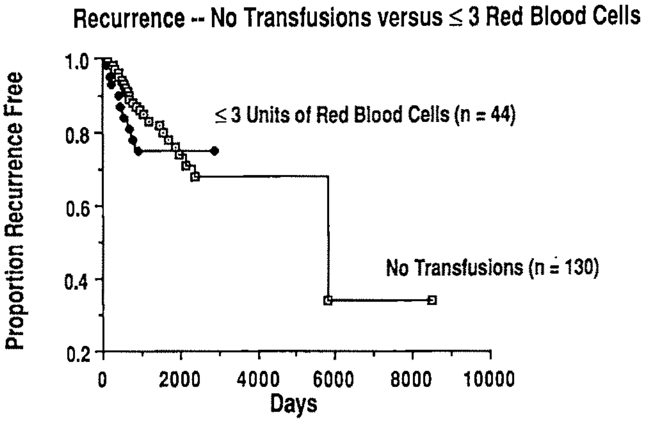

FIG. 5. The Kaplan-Meier plots for the estimated time to recurrence are compared for patients with cervical and colorectal cancers receiving ≤3 units of red blood cells and for patients receiving no transfusions (the prostate cancer patients are not included in these data as only five patients received ≤3 units of red blood cells). These curves are not significantly different from each other (p = 0.15, 0.31). The plots for estimated survival time are similar to these shown for recurrence and not significantly different (data not shown) (p = 0.97, 0.83).

Figure 5 displays a comparison of the unadjusted estimated time to recurrence in colorectal and cervical cancer patients who received ≤3 units of red blood cells and those patients with these cancers who received no blood transfusions. The differences are not significant (p = 0.15; 0.31). The results for comparisons of the estimated time to death due to cancer were similarly not significantly different (data not shown, p = 0.97; 0.83). Figure 6 shows a similar comparison for patients receiving ≤3 units of blood including at least 1 unit of whole blood and for the same group of patients shown in Figure 5 who were not transfused. The results in these two groups are significantly different (p = 0.0009; 0.002).

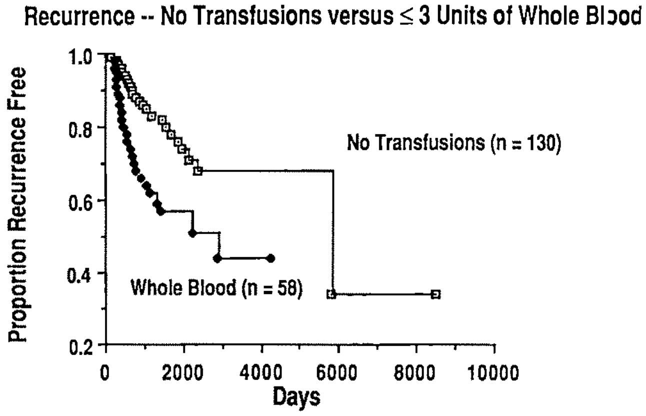

FIG. 6. The Kaplan-Meier plots for the estimated time to recurrence are compared for patients with cervical and colorectal cancers receiving a total of ≤3 units of blood including at least 1 unit of whole blood, and for patients receiving no transfusions (the prostate cancer patients are not included in these data). These curves are significantly different from each other (p = 0.0009, 0.002). The plots for estimated survival time are similar to these shown for recurrence and are significantly different (data not shown) (p = 0.0004, 0.0002).

Virtually identical results were obtained when survival times were estimated ($p < 0.001$; data not shown).

The factors that were significantly associated at the $p < 0.05$ level with earlier recurrence in the initial Cox regression analysis of patients receiving ≤3 units of red blood cells or no transfusions were older age, cervical cancer, and surgical duration of 2–3 hours. When transfusion type (*i.e.*, no transfusions vs. ≤3 units of red blood cells) was added back to this model, no statistically significant increase in the log-likelihood of recurrence or death was found after adjustment for the aforementioned prognostic variables ($p = 0.50$). Thus, transfusion status was not a significant independent predictor of time to recurrence in patients receiving only red blood cells in amounts ≤3 units or no transfusions. A Cox regression to determine which of the prognostic factors were significantly associated with shorter survival times demonstrated that only year of initial diagnosis was a significant predictor of survival time. Diagnosis prior to 1975 was significantly associated with death due to cancer. When transfusion status was added back to the model the contribution of this variable to prediction of cancer-related death was not significant ($p = 0.65$).

A similar Cox regression analysis was performed including patients receiving ≤3 units of whole blood and the aforementioned group of nontransfused patients. The significant predictors of earlier recurrence included low admission hematocrit (<38), more advanced clinical or histologic stage (intermediate and advanced stages), and surgery duration of 2–3 hours. After transfusion type was added back to this model, whole blood transfusion was an independent and significant predictor of earlier recurrence ($p = 0.003$). Low admission hematocrit, more advanced stage, and surgery duration of 2–3 hours were also associated with earlier death due to cancer in this group of patients (those receiving no transfusions or ≤3 units of whole blood). When the variable representing transfusion type (whole blood *vs.* no transfusions) was added to the regression model for survival time, whole blood transfusion was significantly and independently associated with shorter survival times ($p = 0.02$).

Discussion

These data further characterize the previously reported relationship between the kind and amount of blood transfused perioperatively, and the likelihood of later recurrence of, or death due to cancer. Our retrospective methodology and pooling of data from patients with widely differing tumors creates a risk of confounding factors distorting the analysis. Therefore, it is striking that a clear-cut pattern is evident. Patients with cervical or colorectal cancers receiving even 1 whole blood transfusion appear at markedly higher risk of tumor recurrence than patients receiving either ≤3 units of red blood cells or no transfusions at all. This risk is independent of other prognostic factors such as clinical or histologic stage, patient age, anemia, duration of surgery, and year of surgery. In contrast, patients receiving small numbers of transfusions limited to red blood cells did not have significantly worse recurrence or survival experiences than those receiving no transfusions, even when adjusted for other prognostic variables.

These results provide a likely explanation for the conflicting results seen in other retrospective studies of cancer recurrence and blood transfusion.[1-26] Transfusion practices vary greatly among medical centers. Our findings suggest that such variation could dramatically affect the results of analyses that do not take into account the kind of blood component transfused, as well as the number of units of blood transfused.

Employing surrogate markers for surgical complexity (duration of surgery) and tumor invasiveness (clinical and histologic staging), we find no evidence to support the hypothesis that transfusion status is acting as a marker for the tumor's aggressiveness or the clinical state of the patient. In fact, transfused patients with cervical or prostate cancer had somewhat more favorable clinical stage disease, on average, than patients who were not transfused. The best predictors of transfusion are preoperative anemia and lengthier surgeries. Even when these two factors predicting transfusion are adjusted for, transfusion of whole blood is a significant independent predictor of tumor recurrence and death due to cancer. If transfusion status were indeed only a surrogate indicator of tumor invasiveness or a patient's overall clinical condition, it is extremely improbable that this property would be evidenced to such different degrees in recipients of whole blood as opposed to those receiving red cell concentrate transfusions. The most likely explanation for the dramatic differences in outcome between those receiving no transfusions or ≤3 units of red cells and those receiving whole blood is that something present in whole blood modifies the mechanisms that prevent tumor recurrence.

Blood transfusion with plasma-rich components such as whole blood appears to increase the risk of solid tumor recurrence. An immunologic mechanism is most probably at work.[32] As such, transfusions of whole blood, plasma or its components, or large numbers of red cell concentrates should be avoided except when absolutely essential for patient well-being. These points previously have been made by others.[33,34] Obviously, these findings do not in any way argue against the appropriate treatment of significant hemorrhage with the indicated blood components. Severe hemorrhage presents an immediate and clear-cut threat to the patient whereas the risks we have described are long-term and still hypothetical.

Autologous predeposit transfusions also have much to recommend them in the clinical settings we describe. These include a decreased risk of post-transfusion viral infection.[35] There is no evidence that autologous transfusions would ameliorate the deleterious effects of blood transfusion we have proposed. However, if the effect of blood transfusion on outcome after cancer surgery is mediated by exposure to allogeneic antigens in transfused blood, it is reasonable to hope that such effects might be reduced or abrogated by the use of autologous blood transfusions. Given the other compelling reasons for use of autologous blood, its use in perioperative elective transfusions of cancer patients would seem a reasonable strategy, when feasible.

It also appears likely that use of red blood cells washed free of plasma, anticoagulant-preservative solutions, white cell, and platelet debris would mitigate to some degree the postulated effects of transfusion on tumor recurrence, but this remains to be proven in prospective, controlled interventional investigations.

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The Effects of Hespan on Serum and Lymphatic Albumin, Globulin, and Coagulant Protein

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The effects of hydroxyethyl starch (Hespan) resuscitation on serum and lymphatic proteins following hemorrhagic shock were studied in 34 splenectomized dogs. Following shock, five randomly assigned treatment groups received the shed blood plus 50 mL/kg of salt solution (RL) or RL with varying concentrations (0.22–1.5 gm/kg) of Hespan. Each dog received 50 ml/kg/d of the test solution for three days after shock. Prothrombin time, partial thromboplastin time, thrombin time, total serum protein, albumin, globulin, and coagulant protein activity of fibrinogen, prothrombin, and factor VIII were measured before shock, at the end of shock, following resuscitation, and on day 3; thoracic duct lymph values were obtained on day 3. Hespan-supplemented resuscitation lowered all serum proteins including albumin, globulin and coagulant proteins; concomitantly, the lymph protein rose after Hespan resuscitation. This decrease in serum proteins and rise in lymph proteins parallels similar results after albumin resuscitation in man and animals and suggests that Hespan induces an oncotically controlled extravascular protein relocation. Further studies on the significance of these findings need to be conducted.

RESUSCITATION from severe hemorrhagic shock is associated with a reduction in total serum protein (TSP) and serum albumin (SA) concentrations plus a marked rise in obligatory extravascular water sequestration, primarily in the interstitial fluid space.[1,2] Increased capillary permeability after the shock insult is purported to augment this extravascular expansion. Although supplemental albumin therapy has been proposed to counter this capillary leak syndrome,[3] controlled clinical and canine studies show that albumin supplementation induces extravascular protein relocation of all nonalbumin proteins including the globulins, the immunoglobulins, and the coagulant proteins.[4–6] Hespan, a hetastarch with an average molecular weight of 450,000, has been proposed as a more suitable plasma expander.[7,8] Hespan is derived from a waxy starch composed mainly of amylopectin with hydroxyethyl ether introduced into some of the glucose units so that the final product has seven substituted radicals per every ten remaining glucose groups. The end product is stable with a long shelf-life and an intravascular half-life long enough to maintain a colloidal effect for 24–36 hours after infusion. A 6% Hespan solution has colloidal properties similar to albumin. Hespan is slowly metabolized so that about 1% remains in the body after 2 weeks. The usual dose is 30–60 g/d in the averaged size adult. Little data are available on the effects of Hespan on serum protein concentrations and serum protein activity. The present study was designed to determine the effects of Hespan-supplemented resuscitation on serum and lymphatic albumin, globulin, and coagulant proteins.

Materials and Methods

Hespan was studied in 40 male conditioned dogs with an average weight of 22 kg (range: 18–26 kg). Eleven days prior to hemorrhagic shock, splenectomy was performed under general anesthesia using thiamylal sodium injection (11–17.5 mg/kg) and atrophine (0.05 mg/kg) for induction followed by methoxyflurane for light maintenance. Prior to anesthesia baseline measurements were obtained. Following full recovery 11 days later, the animals were again anesthetized. Using sterile technique the femoral artery and vein were cannulated to permit arterial hemorrhage, intermittent blood sampling, and volume restoration as defined by the protocol. A pulmonary artery catheter was positioned through the external jugular vein. Systemic and pulmonary vascular pressures were monitored continuously

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on a previously balanced and calibrated two-channel recorder. The electrocardiogram was continuously monitored.

A modified Wigger's reservior hemorrhagic shock model was used.[6] Following preshock baseline hemodynamic and blood studies, the animals were rapidly bled into a preheparinized (100 units/kg) reservoir to a mean arterial pressure (MAP) of 60 torr and maintained at this level for 90 minutes by appropriate withdrawal or reinfusion of blood. The animals were then rapidly bled to a MAP of 40 torr and maintained at this level for 30 minutes when repeat hemodynamic and blood measurements were made.

After the shock insult, the animals were randomly allocated to five resuscitation groups. The sequence of resuscitation was designed to mimic the clinical setting with each animal receiving 20 mL/kg body weight test solution, the shed blood from the reservoir, and then 30 mL/kg test solution. The test solutions included: (1) lactated Ringers solution (RL); (2) RL with 0.22 g/kg body weight Hespan (RL/H22); (3) RL with 0.45 g/kg Hespan (RL/H45); (4) RL with 0.9 g/kg Hespan (RL/H90); and (5) RL with 1.5 g/kg Hespan (RL/H150). When the last of the test infusion was infused, post resuscitation hemodynamic and serum measurements were repeated. The lines were removed and the animals were returned to their cages and allowed diet as tolerated. Additional test solution (50 mL/kg) was infused daily until the animals were restudied on day 3. The day 3 studies were done with general anesthesia. Besides replacing previous lines, thoracic duct cannulation was added to measure lymphatic flow rates and protein levels. The animals were then killed by the intracardiac injection of potassium chloride and bilateral pneumothoraxes. The hemodynamic and serum parameters measured preshock, after shock, following resuscitation, and on day 3 included systolic, diastolic and MAP, cardiac output, systemic vascular resistence (SVR), and central filling pressure, (PCWP), TSP,[9] SA,[9] ${}_{\text{alpha1}}$-globulin (${}_{\alpha1}$G),[9] ${}_{\text{alpha2}}$-globulin (${}_{\alpha2}$G), betaglobulin (βG), gamma globulin (γG), fibrinogen activity (Ic),[10] prothrombin activity (IIc),[11] coagulant factor VIII activity (VIIIc),[12] plasminogen activity (Pg),[13] antithrombin III activity (ATIIIc).[14] Prothrombin time (PT),[15] activated partial thromboplastin time (PTT),[12] and thrombin time (TT)[16]; thoracic duct protein levels were measured on day 3. Statistical comparisons of the four Hespan supplemented groups to the control RL group were made by multiple ANOVA and Student's t-test where appropriate. Significance was inferred when the level of confidence exceeded 95%.

Results

The shock insult produced similar hemodynamic changes and similar protein changes in all five groups. These changes were almost identical to prior studies with this model.[6]

Following randomization and initiation of resuscitation, six dogs died (none in RL group, one in RL/H22 group, two in RL/H45 group, one in RL/H90 group, and two in RL/H150 group) so that only 34 animals were included in the final statistical analysis. All five resuscitation regimens restored vital signs and peripheral perfusion to predefined resuscitation end points that were not significantly different for each group.

The resuscitation regimen, however, did significantly affect serum protein concentrations. The post resuscitation TSP, SA, and SG levels in RL group averaged 6.5 g/dL, 2.8 g/dL, and 3.7 g/dL, respectively. In contrast, the post resuscitation TSP, SA, and SG levels were significantly lower in all four Hespan groups with the lowest values being 3.3 g/dL, 1.5 g/dL, and 1.6 g/dL, respectively (Table 1). The serum ${}_{\alpha1}$G, ${}_{\alpha2}$G, and the βG fractions were significantly reduced after hespan resuscitation (Table 1). These reductions in serum protein levels remained depressed through the day 3 study in those animals receiving Hespan supplementation (Table 1). Only the βG fraction remained undepressed in the Hespan groups when compared to the RL group. The lymphatic concentrations of proteins rose after Hespan-supplemented resuscitation. The average concentrations of lymphatic total protein (LTP), LA, and LG on day 3 were 2.7 g/dL, 1.3 g/dL, and 1.49 g/dL in the RL group. In contrast, these lymphatic proteins rose after Hespan resuscitation with the highest LTP, LA, and LG on day 3, averaging 4.1 g/dL, 2.0 g/dL, and 2.1 g/dL, respectively (Table 2).

Serum coagulant protein levels paralleled the other serum proteins. The preshock and post shock coagulant protein activity of Ic, IIc, VIIIc, ATIIIc, and Pg were similar in all five groups and were similar to prior studies with this model.[6] The activities of most coagulant proteins were reduced after Hespan resuscitation when compared to the RL group (Table 3). This reduction in the serum coagulant protein activity is reflected by an increase in the PT and PTT following the Hespan resuscitation, with this increase being statistically significant in those animals receiving 1.5 g/kg of Hespan supplementation (Table 3). The serum coagulant protein activity of Ic, IIc, and VIIIc was also decreased after Hespan resuscitation, with this decrease being significant at the higher dosages of Hespan infusion (Table 3). The decrease in the activity of these coagulant proteins is reflected by the increased number of seconds required for specific factor-deficient sera to clot in the Hespan-supplemented animals as compared to the RL group. The serum coagulant activity of ATIIIc and Pg was also decreased following Hespan resuscitation as reflected by a lower activity level in those animals receiving the higher

TABLE 1. *Serum Protein Response to Resuscitation*

Group	RL	RL/H22	RL/H45	RL/H90	RL/H150
TSP (g/dL)					
PR	6.5 ± 1.2	3.3 ± 0.4*	4.1 ± 0.7†	3.8 ± 0.4†	3.3 ± 1.0†
Day 3	5.6 ± 0.9	3.6 ± 0.4†	4.8 ± 0.4*	5.3 ± 0.4	3.9 ± 0.5†
SA (g/dL)					
PR	2.8 ± 0.7	1.7 ± 0.2†	1.9 ± 0.3†	1.6 ± 0.6†	1.5 ± 0.3†
Day 3	2.5 ± 0.6	1.9 ± 0.3†	2.3 ± 0.2	2.5 ± 0.4	1.9 ± 0.4*
α_1G (g/dL)					
PR	0.3 ± 0.01	0.1 ± 0.01*	0.1 ± 0.1*	0.1 ± 0.1†	0.1 ± 0.01†
Day 3	0.3 ± 0.1	0.1 ± 0.03*	0.1 ± 0.1†	0.03 ± 0.01†	0.1 ± 0.02†
α_2G (g/dL)					
PR	1.0 ± 0.3	0.3 ± 0.03†	0.4 ± 0.1†	0.2 ± 0.2†	0.3 ± 0.2†
Day 3	0.8 ± 0.2	0.4 ± 0.1†	0.5 ± 0.1†	0.1 ± 0.1†	0.4 ± 0.1†
βG (g/dL)					
PR	0.8 ± 0.3	0.9 ± 0.2	1.0 ± 0.3	0.6 ± 0.1	0.6 ± 0.1
Day 3	0.8 ± 0.3	0.8 ± 0.1	1.1 ± 0.1*	0.8 ± 0.2	0.6 ± 0.4
γG (g/dL)					
PR	1.6 ± 0.1	0.4 ± 0.2	0.7 ± 0.2†	1.4 ± 0.5	0.7 ± 0.4†
Day 3	1.4 ± 0.3	0.5 ± 0.1†	0.8 ± 0.3†	1.9 ± 0.5	0.6 ± 0.2†

Values are given as mean ± SD.
* $P < 0.05$, when compared to RL group.
† $P < 0.005$, when compared to RL group.

dosages of Hespan infusion (Table 3). A similar pattern in the serum coagulant protein activity was seen on day 3, with a significant prolongation in the PT and PTT associated with a reduction in Ic and VIIIc activity within the serum of the Hespan-resuscitated animals when compared to the RL group (Table 3).

The lymphatic concentrations of the coagulant proteins paralleled the LA and LG concentrations in most instances, but the differences between the Hespan resuscitated animals and the RL group often did not reach statistical significance (Table 4). However, there was a significant decrease in the PTT in one of the Hespan-resuscitated groups when compared to the RL group, thus indicating increased activity of the intrinsic coagulation proteins in the lymph of this Hespan group when compared to the RL group. There was also a significant increase in the Pg activity within the lymphatic juice of two of the Hespan-supplemented groups when compared to the RL group. No significant differences were observed in the lymphatic activity of Ic, IIc, or IIIc following the Hespan resuscitation, although there were insignificant increases in the activities of these coagulant proteins when compared to the RL group (Table 4).

Discussion

Prior randomized studies showed that addition of human serum albumin to the resuscitation regimen for hemorrhagic shock in humans increased SA and decreased the serum concentrations of nonalbumin proteins.[5,6] This included a decrease in immunoglobulin protein concentration and a concomitant decrease in coagulant protein concentration and activity.[5,17] This

TABLE 2. *Thoracic Duct Lymph Proteins after Resuscitation*

Group	RL	RL/H22	RL/H45	RL/H90	RL/H150
TSP (g/dL)					
Day 3	2.7 ± 0.6	3.9 ± 0.2†	4.1 ± 0.8†	3.0 ± 0.3	3.1 ± 1.3
SA (g/dL)					
Day 3	1.3 ± 0.3	1.9 ± 0.4*	2.0 ± 0.5*	1.3 ± 0.1	1.6 ± 0.6
α_1G (g/dL)					
Day 3	0.08 ± 0.05	0.1 ± 0.1	0.2 ± 0.1*	0.2 ± 0.1*	0.2 ± 0.1*
α_2G (g/dL)					
Day 3	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.1 ± 0.04	0.3 ± 0.1
βG (g/dL)					
Day 3	0.3 ± 0.1	0.9 ± 0.1†	0.9 ± 0.2†	0.3 ± 0.04	0.4 ± 0.3
γG (g/dL)					
Day 3	0.7 ± 0.2	0.7 ± 0.1	0.7 ± 0.3	1.2 ± 0.2†	0.6 ± 0.4

Values are given as mean ± SD.
* $P < 0.05$, when compared to RL group.
† $P < 0.005$, when compared to RL group.

TABLE 3. *Serum Coagulation Profile after Resuscitation*

Group	RL	RL/H22	RL/H45	RL/H90	RL/H150
PT (s)					
PR	7.1 ± 0.3	7.5 ± 0.6	7.5 ± 0.6	7.4 ± 0.6	8.0 ± 0.6†
Day 3	6.4 ± 0.4	6.1 ± 0.8	6.4 ± 0.4	6.3 ± 0.4	7.2 ± 0.7*
PTT (s)					
PR	18.2 ± 1.5	21.8 ± 2.9†	24.7 ± 13.2	18.8 ± 1.6	25.8 ± 3.7†
Day 3	16.4 ± 1.7	18.9 ± 5.5	16.8 ± 1.0	16.8 ± 0.8	24.1 ± 3.0†
TT (s)					
PR	7.7 ± 0.8	5.1 ± 1.9†	18.3 ± 13.3*	7.7 ± 0.9	5.2 ± 0.4†
Day 3	6.8 ± 0.8	5.5 ± 0.4†	6.8 ± 1.3	5.7 ± 0.4*	4.8 ± 0.2†
Ic (s)					
PR	11.3 ± 2.9	12.9 ± 2.3	13.8 ± 4.1	18.8 ± 5.0†	18.4 ± 5.5†
Day 3	5.6 ± 1.6	9.8 ± 1.9	7.5 ± 1.4	6.3 ± 1.8	10.6 ± 4.0†
IIc (s)					
PR	28.8 ± 1.8	19.1 ± 1.8	20.1 ± 3.9	19.3 ± 1.4	21.5 ± 2.1†
Day 3	25.6 ± 3.4	18.5 ± 2.2	18.5 ± 1.4	17.2 ± 1.3	19.7 ± 1.3
VIIIc (s)					
PR	18.7 ± 1.0	39.0 ± 6.9*	31.4 ± 3.0†	36.8 ± 4.6†	38.3 ± 4.5†
Day 3	16.8 ± 0.9	39.7 ± 8.4	29.8 ± 3.3	27.5 ± 2.0*	40.8 ± 4.7*
AT IIIc (units/mL)					
PR	104 ± 13	100 ± 38	72 ± 14*	89 ± 20	81 ± 15*
Day 3	117 ± 20	94 ± 23*	89 ± 13*	122 ± 12	90 ± 28*
Pg (CTA/units/mL)					
PR	2.9 ± 0.3	2.8 ± 0.1	2.8 ± 0.4	2.7 ± 0.3	2.0 ± 0.1†
Day 3	2.9 ± 0.2	3.0 ± 0.1	3.0 ± 0.3	2.8 ± 0.3	2.9 ± 0.3

Values are given as mean ± SD. When coagulation data are presented in seconds required for specific factor deficient sera to clot, the activity of the specific clotting factor is inversely related to prolongation in clot formation.

* $P < 0.05$, when compared to RL group.

† $P < 0.005$, when compared to RL group.

latter decrease was associated with an increase in the number of blood transfusions needed to achieve the same red cell mass as the injured patients not receiving albumin supplementation.[6] The reduction in serum coagulant protein concentration and activity after albumin have been reproduced in dogs subjected to the same hemorrhagic shock insult reported herein.[4] Later studies showed that dogs receiving albumin supplementation had an increase in lymphatic protein concentration of the nonalbumin proteins.[18] This increased vascular efflux of nonalbumin proteins after albumin may result from an oncotic factor designed to maintain the optimal lymph:plasma protein ratio.[18] In theory, this optimal lymph:plasma protein ratio may be different for specific proteins depending upon molecular weight and geometric configuration and also for the specific time in the

TABLE 4. *Lymph Coagulation Profile after Resuscitation*

Group	RL	RL/H22	RL/H45	RL/H90	RL/H150
PT (s)					
Day 3	8.7 ± 1.1	8.5 ± 1.2	8.9 ± 2.0	8.3 ± 0.4	9.6 ± 0.7
PTT (s)					
Day 3	34.8 ± 7.3	30.2 ± 12.4	27.4 ± 10.2	25.3 ± 3.3*	39.8 ± 10
TT (s)					
Day 3	8.3 ± 1.9	7.1 ± 0.5	8.0 ± 2.3	6.8 ± 0.9	6.2 ± 1.3*
Ic (mg/dL)					
Day 3	34.9 ± 3.4	21.0 ± 3.8	26.7 ± 22.5	19.5 ± 3.7	21.2 ± 11.5
IIc (% normal)					
Day 3	39.6 ± 8.1	22.6 ± 7.5	23.4 ± 2.3	20.6 ± 3.9	25.1 ± 0.8
VIIIc (% normal)					
Day 3	24.0 ± 3.1	39.9 ± 5.2	37.0 ± 4.3	37.4 ± 3.1	29.8 ± 16.9
AT IIIc (mg/dL)					
Day 3	66.4 ± 23.1	82 ± 18	79 ± 14	74 ± 10	67 ± 10
Pg (CTA units/mL)					
Day 3	2.7 ± 0.1	2.9 ± 1.0*	2.4 ± 0.3*	2.6 ± 0.1	2.8 ± 0.1

Values are given as mean ± SD. When coagulation data are presented in seconds required for specific factor deficient sera to clot, the activity of the specific clotting factor is inversely related to prolongation in clot formation.

* $P < 0.05$ when compared to RL group.

multiphasic response to the hemorrhagic shock insult.[18] Few studies have serially monitored the lymph:plasma ratios of specific proteins after resuscitation from hemorrhagic shock so that an optimal ratio for a coagulant protein, an immunoglobulin, or any other nonalbumin protein exists only in theory. A more thorough understanding of the total shock insult mandates a more sophisticated approach to the total body protein changes during and after resuscitation.

Pending such studies, serial measurements of serum proteins provide the only guide to the efficacy of a resuscitation regimen. The present study reinforces the theory that the intravascular addition of any colloidal particle induces relocation of proteins into the interstitial fluid space, persumably to maintain a specific lymph to plasma oncotic balance. This is the first time that this relocation has been demonstrated after Hespan-supplemented resuscitation. This extravascular oncotic relocation included movement of the Hespan particles. Although Hespan concentrations were not measured, the lymph had increased particulate matter, with the greatest optical density seen in those animals that received the largest amount of Hespan. Thus, the oncotic factor leading to the extravascular relocation of oncotic particles drives all oncotic particles, including proteins and Hespan, from the capillary into the interstitial fluid space and then into the lymphatic channels. The end result is a decrease in all serum protein levels including, TSP, SA, SG, and the coagulant proteins. Although the significance of this reduction in coagulant protein activity was not fully tested herein, similar changes in man after albumin resuscitation were associated with the need for additional blood transfusions to achieve the same red cell mass as seen in patients not receiving albumin.[5] The clinical effects of reduced intravascular protein after Hespan resuscitation needs to be assessed in controlled studies. Pending such studies, Hespan-supplemented resuscitation should be suspected for causing multiple alterations in circulatory protein concentrations and functions due to an oncotically controlled extravascular protein relocation.

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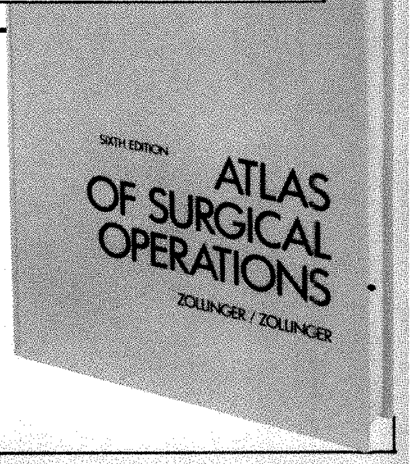

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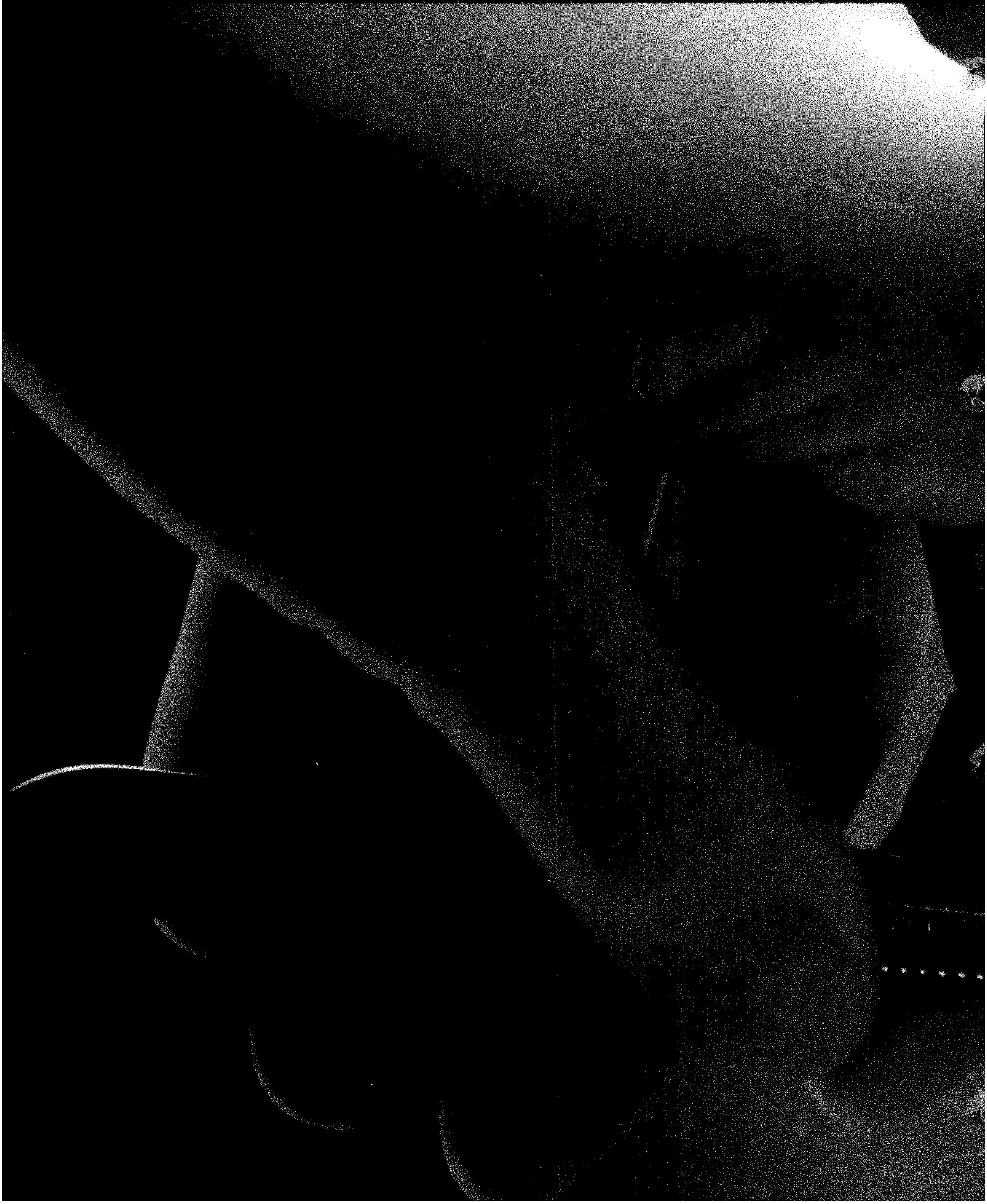

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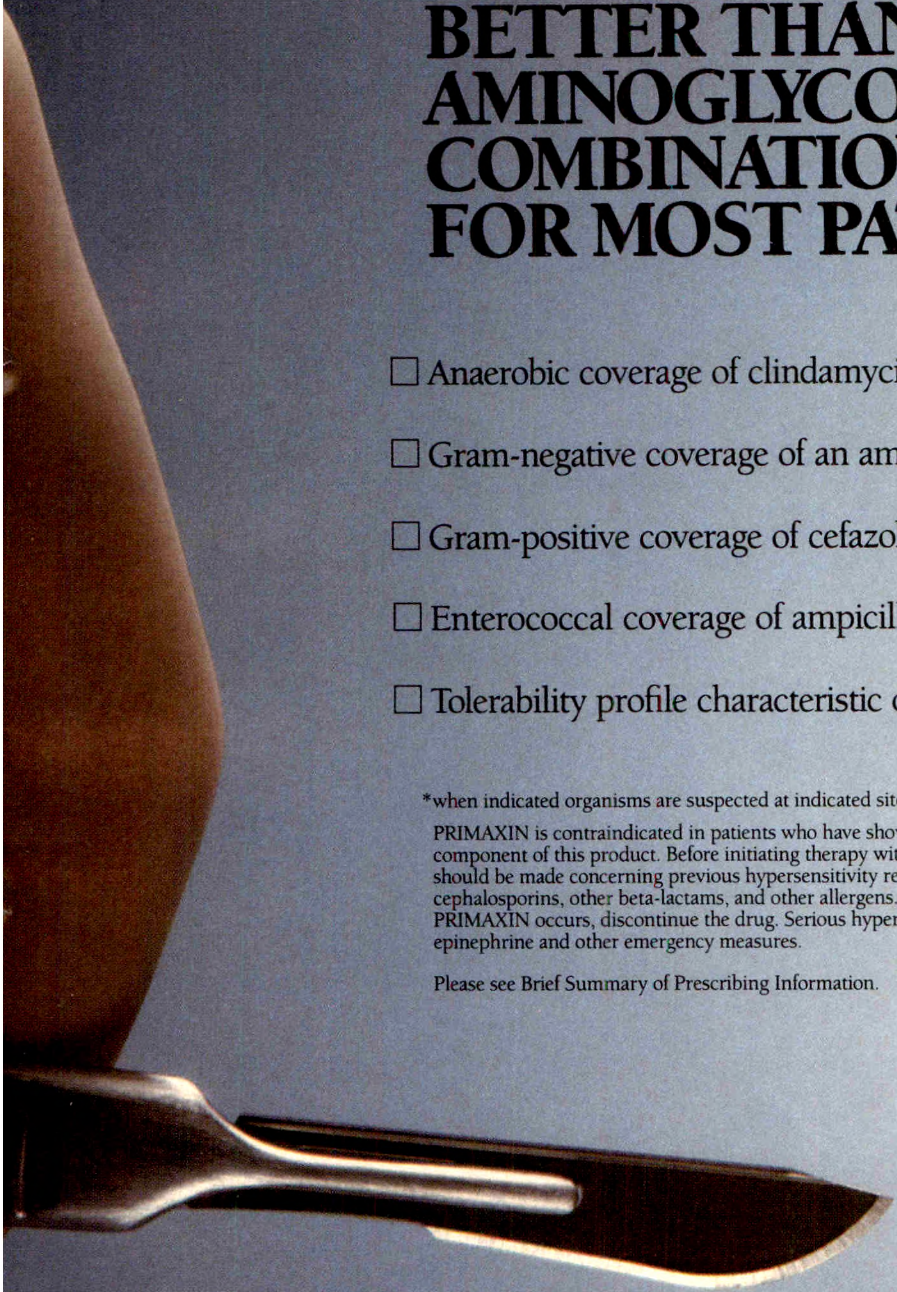

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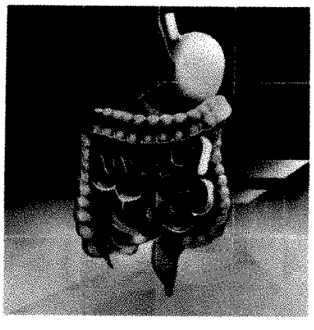

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THERE HAVE BEEN REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER BETA LACTAM. BEFORE INITIATING THERAPY WITH 'PRIMAXIN,' CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA LACTAMS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION TO 'PRIMAXIN' OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with virtually all antibiotics, including PRIMAXIN; therefore it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. This colitis may range in severity from mild to life threatening.

Mild cases of pseudomembranous colitis may respond to drug discontinuance alone. In more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte, and protein supplementation, and the use of a drug such as oral vancomycin, as indicated. Isolation of the patient may be advisable. Other causes of colitis should also be considered.

Precautions: *General*—CNS adverse experiences such as confusional states, myoclonic activity, and seizures have been reported during treatment with PRIMAXIN, especially when recommended dosages were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. However, there have been reports of CNS adverse experiences in patients who had no recognized or documented underlying CNS disorder or compromised renal function.

Patients with severe or marked impairment of renal function, whether or not undergoing hemodialysis, had a higher risk of seizure activity when receiving maximum recommended doses than those with no impairment of renal function; therefore, maximum recommended doses should be used only where clearly indicated (see DOSAGE AND ADMINISTRATION).

Patients with creatinine clearances of ≤ 5 mL/min/1.73 m^2 should not receive PRIMAXIN unless hemodialysis is instituted within 48 hours.

For patients on hemodialysis, PRIMAXIN is recommended only when the benefit outweighs the potential risk of seizures.

Close adherence to the recommended dosage and dosage schedules is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of PRIMAXIN re-examined to determine whether it should be decreased or the antibiotic discontinued.

As with other antibiotics, prolonged use of PRIMAXIN may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken. While PRIMAXIN possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system function during prolonged therapy is advisable.

Drug Interactions—Since concomitant administration of PRIMAXIN and probenecid results in only minimal increases in plasma levels of imipenem and plasma half-life, it is not recommended that probenecid be given with PRIMAXIN.

PRIMAXIN should not be mixed with or physically added to other antibiotics. However, PRIMAXIN may be administered concomitantly with other antibiotics, such as aminoglycosides.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Gene toxicity studies were performed in a variety of bacterial and mammalian tests *in vivo* and *in vitro*. The tests were: V79 mammalian cell mutation assay (PRIMAXIN alone and imipenem alone), Ames test (cilastatin sodium alone), unscheduled DNA synthesis assay (PRIMAXIN), and *in vivo* mouse cytogenicity test (PRIMAXIN). None of these tests showed any evidence of genetic damage.

Reproduction tests in male and female rats were performed with PRIMAXIN at dosage levels up to 8 times the usual human dose. Slight decreases in live fetal body weight were restricted to the highest dosage level. No other adverse effects were observed on fertility, reproductive performance, fetal viability, growth, or postnatal development of pups. Similarly, no adverse effects on the fetus or on lactation were observed when PRIMAXIN was administered to rats late in gestation.

Pregnancy—Pregnancy Category C: Teratogenicity studies with cilastatin sodium in rabbits and rats at 10 and 33 times the usual human dose, respectively, showed no evidence of adverse effect on the fetus. No evidence of teratogenicity or adverse effect on postnatal growth or behavior was observed in rats given imipenem at dosage levels up to 30 times the usual human dose. Similarly, no evidence of adverse effect on the fetus was observed in teratology studies in rabbits with imipenem at dosage levels at the usual human dose.

Teratology studies with PRIMAXIN at doses up to 11 times the usual human dose in pregnant mice and rats during the period of major organogenesis revealed no evidence of teratogenicity.

Data from preliminary studies suggest an apparent intolerance to PRIMAXIN (including emesis, inappetence, body weight loss, diarrhea, and death) at doses equivalent to the average human dose in pregnant rabbits and cynomolgus monkeys that is not seen in non-pregnant animals in these or other species. In other studies, PRIMAXIN was well tolerated in equivalent or higher doses (up to 11 times the average human dose) in pregnant rats and mice. Further studies are under way to evaluate these findings.

There are, however, no adequate and well-controlled studies in pregnant women. PRIMAXIN should be used only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRIMAXIN is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in infants and children below 12 years of age have not yet been established.

Adverse Reactions: PRIMAXIN is generally well tolerated. Many of the 1,723 patients treated in clinical trials were severely ill and had multiple background diseases and physiological impairments, making it difficult to determine causal relationship of adverse experiences to therapy with PRIMAXIN.

Local Adverse Reactions—Local adverse clinical reactions that were reported as possibly, probably, or definitely related to therapy with PRIMAXIN were: phlebitis/thrombophlebitis (3.1%), pain at the injection site (0.7%), erythema at the injection site (0.4%), vein induration (0.2%), infused vein infection (0.1%).

Systemic Adverse Reactions—The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to PRIMAXIN were: nausea (2.0%), diarrhea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%) (see PRECAUTIONS), dizziness (0.3%), pruritus (0.3%), urticaria (0.2%), somnolence (0.2%).

Additional adverse systemic clinical reactions reported as possibly, probably, or definitely drug related occurring in less than 0.2% of the patients or reported since the drug was marketed are listed within each body system in order of decreasing severity: *Gastrointestinal*—pseudomembranous colitis (see WARNINGS), hemorrhagic colitis, gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, heartburn, pharyngeal pain, increased salivation; *CNS*—encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, psychic disturbances; *Special Senses*—transient hearing loss in patients with impaired hearing, tinnitus; *Respiratory*—chest discomfort, dyspnea, hyperventilation, thoracic spine pain; *Cardiovascular*—palpitations, tachycardia; *Renal*—oliguria/anuria, polyuria; *Skin*—erythema multiforme, facial edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae; *Body as a Whole*—polyarthralgia, asthenia/weakness.

Adverse Laboratory Changes—Adverse laboratory changes without regard to drug relationship that were reported during clinical trials or reported since the drug was marketed were: *Hepatic*—increased SGPT, SGOT, alkaline phosphatase, bilirubin, and LDH; *Hemic*—increased eosinophils, positive Coombs test, decreased WBC and neutrophils, including agranulocytosis, increased WBC, increased platelets, decreased platelets, decreased hemoglobin and hematocrit, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils; *Electrolytes*—decreased serum sodium, increased potassium, increased chloride; *Renal*—increased BUN, creatinine; *Urinalysis*—presence of urine protein, urine red blood cells, urine white blood cells, urine casts, urine bilirubin, and urine urobilinogen.

NOTE: Due to the high antimicrobial activity of PRIMAXIN, it is recommended that the maximum total daily dosage not exceed 50 mg/kg/day or 4.0 g/day, whichever is lower.

How Supplied: PRIMAXIN is supplied as a sterile powder mixture in vials, infusion bottles, and single-dose ADD-Vantage®*† vials containing imipenem anhydrous and cilastatin sodium as follows: 250 mg imipenem equivalent and 250 mg cilastatin equivalent; 500 mg imipenem equivalent and 500 mg cilastatin equivalent.

Caution: The suspension from vials is not for direct infusion.

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A Kinetic Study of Leucine Metabolism in Severely Burned Patients

Comparison Between a Conventional and Branched-Chain Amino Acid–Enriched Nutritional Therapy

YONG-MING YU, M.D., DAVID A. WAGNER, PH.D., J. C. WALESRESWSKI, M.D.,
JOHN F. BURKE, M.D., and VERNON R. YOUNG, PH.D., D.SC.

A cross-over design study was used to examine the metabolic consequences of enteral feeding for 48 to 96 hours with either a branched-chain amino acid (BCAA)-enriched (44% BCAA) or a conventional egg protein formulation in 12 severely burned adult patients. A stable isotope labeled leucine (L-1-^{13}C-leucine) tracer approach was used to measure leucine flux and oxidation and to estimate rates of whole body protein synthesis and breakdown. Additionally, $^{15}N_2$-urea and 6,6-^{2}H-glucose were administered to assess the status of urea and glucose kinetics with these two nutritional treatments. Average patient age was 54 years, and average burn surface area was 36%. Studies were conducted at an average of 25 days postburn. Leucine flux and oxidation were significantly ($p < 0.01$, by paired t-test) elevated with BCAA feeding as compared to the egg protein formulation. However, there were no significant differences in the rates of leucine incorporation into, or release from, proteins ($p > 0.05$) between the two dietary periods. Mean rates of body protein synthesis and breakdown for each diet were about twice the rates reported for healthy young adults. Apparent nitrogen balance measurements were not statistically different ($p > 0.1$) between the two diet periods. Furthermore, urea and glucose kinetics failed to show significant differences between the two diet periods. It appears from these results that the major consequences of increased intake of leucine from the BCAA formula is an enhanced rate of leucine oxidation. In conclusion, (1) the availability of BCAAs is not rate-limiting for enhanced protein synthesis in burn patients, and (2) the use of enriched BCAA formulas in burn therapy does not appear to offer advantages over a routinely used enteral egg protein formula, at least based on the present determinations.

From the Department of Surgery, Massachusetts General Hospital and Shriners Burns Institute, Boston, Massachusetts, and the Laboratory of Human Nutrition, Department of Applied Biological Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts

MAJOR THERMAL INJURY metabolism is characterized by an increased rate of body protein breakdown and elevated energy expenditure,[1] impaired use of glucose,[2,3] and alterations in the metabolism of lipid substrates.[4,5] A number of studies have suggested that increasing the exogenous supply of branched-chain amino acids (BCAAs) might minimize the overall catabolic state under conditions of severe trauma and that this would be of benefit in the overall treatment of trauma patients (*e.g.*,[6–8]). This has been proposed, in part, because (1) leucine has been shown to promote protein synthesis and inhibit protein breakdown when the amino acid is added to incubated muscle preparations,[9,10] and (2) there is an increased rate of BCAA oxidation in trauma patients, possibly creating a deficit in the availability of leucine for purposes of meeting substrate needs for protein synthesis.[11] To date, studies conducted to evaluate the possible advantages of supplying BCAA-enriched nutritional formulations to trauma patients have mainly utilized the nitrogen balance technique,[12,13] as well as monitoring amino acid profiles in blood and the arteriovenous-amino acid concentration differences across the limbs.[14–16] However, the findings so far have been inconsistent,[17,18] and there have been no studies designed to directly explore the aforementioned hypothesis.

The present study used a stable isotope labeled leucine (L-1-^{13}C-leucine) tracer approach and a cross-over design to examine the metabolic consequences of using a BCAA-enriched enteral feeding, as compared to a conventional egg protein formulation, in 12 severely burned patients. In addition, the tracers $^{15}N_2$-urea and 6,6-^{2}H-glucose were used in seven of these 12 patients to assess the status of urea and glucose kinetics under the two conditions of nutritional support. Using these tech-

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Supported by Grant Nos. GM 21700 and DK 15856 from the National Institutes of Health, and a grant-in-aid from the Shriners Burn Institute, Boston, Massachusetts.

Reprint requests and correspondence: Vernon R. Young, Ph.D., D.Sc., Massachusetts Institute of Technology, 77 Massachusetts Avenue, Room 56-333, Cambridge, MA 02139.

Submitted for publication: September 17, 1987.

TABLE 1. *General Condition of the Burn Patients*

Patient No.	Sex	Age	IBW (kg)	% BSA Burned	PBD	% Open Wound at Study
1 (II)	M	64	75.9	35	50.0	11.5
2 (I)	M	46	85.0	60	45.0	29.0
3 (I)	M	56	73.6	40	16.0	23.0
4 (II)	F	21	58.0	35	9.0	35.0
5 (I)	F	54	59.5	15	27.0	12.0
6 (I)	M	61	75.9	60	33.0	0.0
7 (II)	M	35	66.0	42	35.0	5.0
8 (I)	M	54	74.0	10	14.0	8.0
9 (II)	M	41	77.7	60	10.0	16.0
10 (I)	F	82	52.7	25	16.0	0.0
11 (II)	F	74	50.0	20	8.0	15.0
12 (II)	F	60	61.8	25	32.0	0.0
Mean		54	67.5	36	25.0	12.9
SEM		5	3.7	5	4.0	3.3

Values in parentheses refer to the order in which BCAA was received, namely, either during first (I) or second (II) period.

IBW = ideal body weight based on 1959 Metropolitan Life Insurance Company Tables.

BSA = burn surface area.

PBD = postburn days.

niques we were able to investigate whether a BCAA-enriched diet improves net protein balance in burn patients and, if so, whether this was achieved by a stimulation of protein synthesis and/or inhibition of body protein breakdown.

Materials and Methods

Materials

L-1-^{13}C-leucine (99% ^{13}C), ^{15}N-urea (99%, ^{15}N), and 6,6-^{2}H-glucose (98% ^{2}H) were purchased from KOR Isotopes, Cambridge, MA and $NaH^{13}CO_3$ (99% ^{13}C) from Prochem, Summit, NJ. Solid whole egg and egg white were obtained from the dietary department of the Massachusetts General Hospital. The BCAA-enriched amino acid mixture, carbohydrate, fat, trace mineral, and vitamin supplements used for the enteral formulation were obtained from a commercial supplier (Sandoz Nutrition Corporation, Minneapolis, MN). The isotopes were prepared and infused, using sterile techniques after having been proved sterile and pyrogen-free as previously described.[19]

Patients

Twelve severely burned patients participated in this study. Written consent was obtained from each patient after they were carefully informed of the purpose, design, and possible hazards of the experiment. Clinical details for the patients are given in Table 1.

Study Design

Each study was performed when the patient was in a relatively stable condition, as demonstrated by stable vital signs, including blood pressure, respiration rate, oral temperature, normal liver and kidney function, and absence of clinical signs of general infection and septicemia.

A cross-over experimental design was used, with each patient being studied during two consecutive dietary periods. One of these involved an egg and carbohydrate enteral feeding regimen of the kind routinely used at this center; the other was a BCAA-enriched enteral feeding formulation. Each dietary period lasted 48–96 hours (Fig. 1), at the end of which a 2-hour stable isotope infusion study was performed. The order in which the patients received the two nutritional support systems was random. The patients had received an enteral feed-

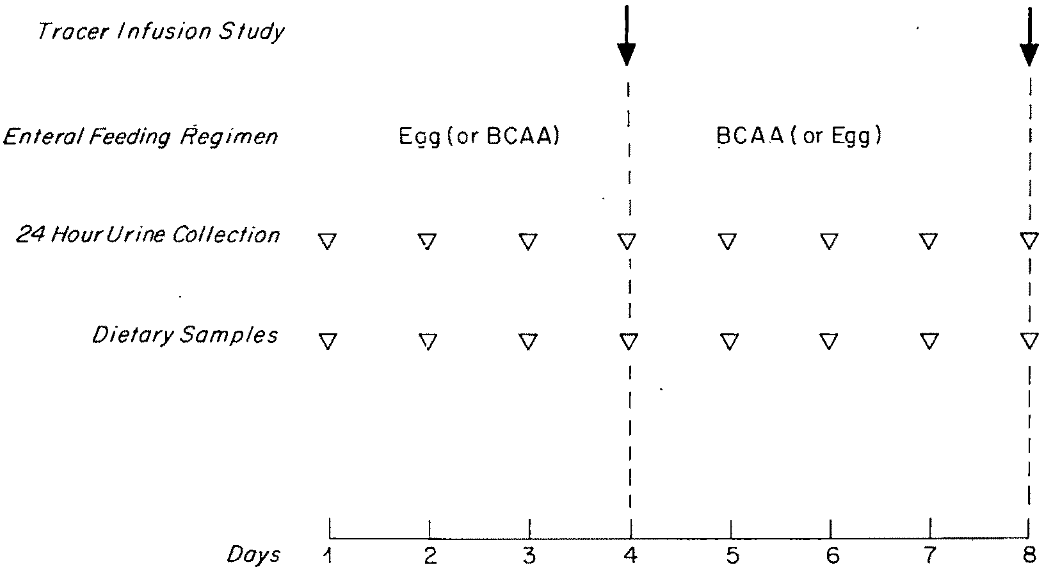

FIG. 1. Schematic outline of study design. Each patient was studied during two dietary periods, one being a BCAA-enriched formula and the other based on an egg protein. Each diet period lasted 2–4 days.

ing of a conventional egg-protein-polycose diet for at least 5 days before the cross-over study began. The amounts of nitrogen and energy supplied during this earlier period were essentially the same as during the experimental period. The experimental protocol was approved by the Human Study Committee of the Massachusetts General Hospital. A graphic description of the major features of the experimental design is given in Figure 1.

Enteral Feeding Regimens

Two nutritional formulations were used in the present study (Table 2). The principal difference between the two diets is related to the composition of the protein source: (1) a mixture of egg white and whole egg powder, containing about 20% (w/w) of BCAA, or (2) a BCAA-enriched amino acid mixture, containing 44% (w/w) of BCAA (Table 3). Nitrogen intake was 0.26 ± 0.02 gN $kg^{-1} \times d^{-1}$ for the egg diet and 0.24 ± 0.02 gN $kg^{-1} \times d^{-1}$ for the BCAA diet. Average energy intakes for each diet period were (mean ± SEM), 40 ± 3 kcal $\times kg^{-1} \times d^{-1}$ for the egg diet and 40 ± 2 kcal $kg^{-1} \times d^{-1}$ for the BCAA diet. Carbohydrate intake was calculated to be equivalent to about 5 mg glucose $kg^{-1} \times min^{-1}$, with the remainder of the energy being supplied by fat. The diets were prepared in the dietary department of Massachusetts General Hospital. Both diets were administered enterally via an indwelling nasogastric tube, using an infusion pump (Model 927, IMED Corporation, San Diego, CA).

Infusion Studies

All tracer studies were conducted while the patients were in the fed state. The isotopes were infused through an existing central venous catheter and blood samples were withdrawn from previously placed arterial lines. Before the isotope infusion period was started, blood and expired air samples were taken for measurement of background isotope enrichments of leucine, α-ketoisocaproate (KIC), urea, and glucose in the plasma and of $^{13}CO_2$ in the expired air. Then, the primed-constant infusions of L-1-^{13}C-leucine, $^{15}N_2$-urea, and 6,6-^{2}H-glucose were started, together with a simultaneous priming dose of $NaH^{13}CO_3$ (9.2 μmol). The approximate, but known, infusion rates of the isotopic tracers were 0.65 mmol $\times h^{-1}$ for L-1-^{13}C-leucine, 1.2 mmol $\times h^{-1}$ for $^{15}N_2$-urea, and 1.2 mmol $\times h^{-1}$ for 6,6-^{2}H-glucose. The priming doses for these tracers were 0.65 mmol, 12 mmol, and 1.6 mmol, respectively. The isotope infusion period lasted for 120 minutes. Additional details have been described earlier,[19] and a schematic outline of the tracer infusion protocol is shown in Figure 2.

TABLE 2. *Composition of the Egg Protein and Amino Acid Based Enteral Diets*

Component	Egg Diet	BCAA Diet
Amino acid mixture*	—	1.82 ± 0.15
Total egg powder (dried)	3.25 ± 0.19	—
% Dried whole egg powder (w/w)	59.80 ± 4.80	—
% Dried egg white (w/w)	40.20 ± 4.80	—
Lipid†	—	0.78 ± 0.07
Polycose‡	5.34 ± 0.39	6.44 ± 0.42
Vitamin§	1 Packet	1 Packet
Mineral‖	1 Packet	1 Packet

Values are expressed as g $\times kg^{-1}d^{-1}$ (mean ± SEM).

* Nutrisource Amino Acid Powder (15.4 g packet).

† Nutrisource Lipid (contains 20% of fat as median chain triglycerides).

‡ Ross Laboratories, Columbus, OH 43316.

§ Nutrisource Vitamins, 10 g powder, which provides 100% of the NRC-RDA for vitamins per packet. The information on composition is provided by the Technical Manual of Nutrisource, Sandoz Nutrition Corporation, Minneapolis, MN, p 9.

‖ Nutrisource Minerals 24 g powder, which provides 100% of the NRC-RDA for minerals and recommended safe and adequate intakes of the newly recognized trace minerals. The information on composition is provided by the Technical Manual of Nutrisource, Sandoz Nutrition Corporation, p 10.

Analytic Methods

The isotopic enrichment of leucine was determined by isolation of the free amino acid from plasma and derivatization to the N-acetyl, n-propyl (NAP) ester.[20] The L-1-^{13}C-leucine was analyzed on a Hewlett-Packard 5985B quadruple mass spectrometer, using positive chemical ionization with methane as the reagent gas, with selected ion monitoring at $M/Z = 216$ and 217. A 12-m × 0.20 mm ID, OV-1 capillary column, using helium as a carrier gas, was used in the gas chromato-

TABLE 3. *Amino Acid Composition of Egg Proteins and of the BCAA Mixture*

Amino Acid	Whole Egg (g/100 g protein)	Egg White (g/100 g protein)	BCAA Mixture (g/100 g amino acids)
Isoleucine	5.1	5.5	11.0
Leucine	8.8	9.4	22.0
Valine	6.5	7.4	11.0
Tryptophan	1.8	1.7	1.5
Phenylalanine	5.5	6.7	4.0
Methionine	1.1	2.3	3.0
Lysine	7.3	7.7	6.5
Threonine	5.2	5.1	5.0
Arginine	6.7	6.3	7.0
Tyrosine	4.3	4.4	0.7
Cystine	1.8	2.5	1.0
Alanine	5.9	6.6	5.5
Glutamic Acid	12.6	10.3	7.8
Aspartic Acid	9.1	5.9	3.5
Histidine	2.2	2.1	3.5
Serine	8.2	7.3	2.0
Glycine	3.6	4.0	3.0
Proline	4.1	4.0	2.0

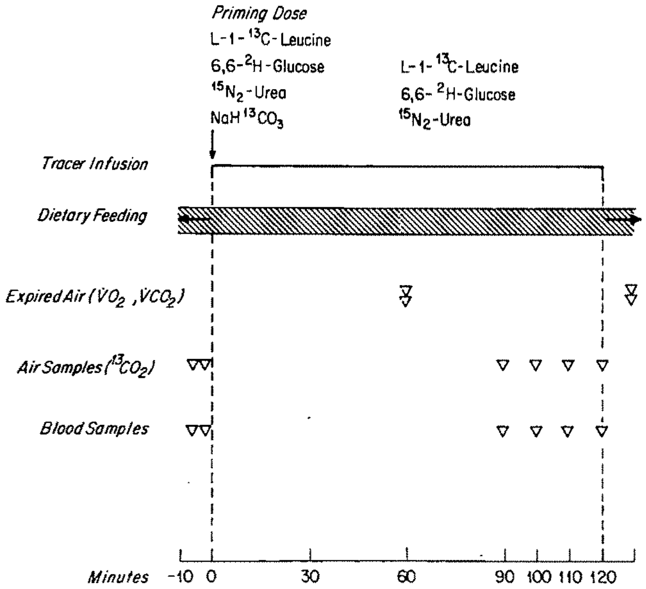

FIG. 2. Schematic outline of tracer infusion protocol. The total infusion period was 120 minutes. For the isotopic plateau level, plasma and air samples were collected between 90 and 120 minutes.

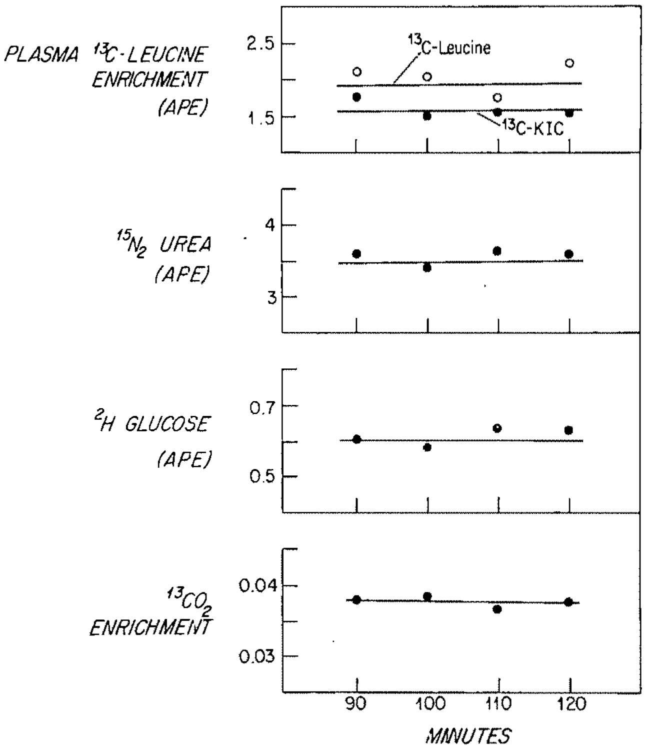

FIG. 3. An example of the plateau level of isotope enrichments for L-1-^{13}C-leucine, 1-^{13}C-KIC, ^{15}N-urea, 6,6-^{2}H-glucose in plasma, and $^{13}CO_2$ enrichment in expired air for one patient.

graph. The enrichment of the isotope was calculated according to Matthews et al.[21] α-Ketoisocaproic acid was isolated from the same plasma sample as those used for leucine analysis. L-1-^{13}C-Ketoisocaproic acid was determined by conversion to a t-butyl-silylquinoxalinol derivative. This is a slight modification of a previously published method,[22] with the t-butyl-silyl group formed by the addition of MTBSTFA (Pierce Chemical Company, Rockford, IL) rather than BSTFA. Electron impact ionization was used on a Hewlett-Packard 5970 instrument, with selected ion monitoring of $M/Z = 259$ and 260 [MW-57 for unlabeled and labeled α-ketoisocaproic acid]. A similar capillary column for the gas chromatography was used as described previously. The deuterated glucose[23] and $^{15}N_2$-urea samples[24] were analyzed by electron impact ionization, as described previously.

Enrichments of all compounds were calculated as atom per cent excess, relative to natural background levels of isotope. All samples were run in duplicate. If the results did not reproduce within 5%, the samples were reinjected two additional times.

Expired air samples were used to measure VO_2 and VCO_2 levels, as described previously.[19] Air samples were analyzed for $^{13}CO_2$ enrichment, using a dual collector isotope ratio mass spectrometer (Nuclide Corp., State College, PA). Atom per cent excess (APE) of $^{13}CO_2$ was determined relative to the reference carbon dioxide derived from potassium carbonate. The baseline $^{13}CO_2$ values were subtracted from each plateau sample to give a relative atom per cent excess $^{13}CO_2$.

Amino acid concentrations in plasma and infusates were measured by conventional automated ion-exchange chromatography with the aid of an automated amino acid analyzer (Model 119 CL, Beckman Instruments, Palo Alto, CA).

Complete urine samples were collected and pooled for each 24 hours and the total volume was recorded. The concentration of urinary creatinine was determined,[25] and the total nitogen content of urine and diets was measured by the Kjeldahl method.[26] The amino acid composition of the whole egg and egg white solids was determined through the courtesy of Dr. C. E. Bodwell, USDA Human Nutrition Institute, Beltsville, MD.

Calculations

In all of the tracer experiments, isotopic equilibrium appeared to be reached within 90 minutes, as demonstrated by a stable level of isotope enrichment in plasma of L-1-^{13}C-leucine, 1-^{13}C-KIC, $^{15}N_2$-urea, and 6,6-^{2}H-glucose and $^{13}CO_2$ in expired air (*e.g.*, Fig. 3). Therefore, the equations used for the calculations of leucine, glucose, and urea fluxes were based on steady-state conditions.

In order to take into account the differences between the isotopic abundance of plasma-free leucine and that of the intracellular precursor pool,[27] the whole body leucine flux was calculated from measurements of plasma 1-^{13}C-KIC enrichment,[27–29] according to the following equation[30]:

$$Ra_{leu} = \left(\frac{Ei}{Ep} - 1\right) i,$$

where Ra = plasma leucine flux (μmol × kg^{-1} × h^{-1}), Ei = the ^{13}C-leucine enrichment in the infusate (APE), Ep = plasma 1-^{13}C-KIC enrichment (APE), and i = the rate of isotope infusion (μmol kg^{-1} × h^{-1}).

The same general equation was applied for estimating urea and glucose fluxes.

The rates of whole body protein synthesis and protein breakdown were calculated assuming an average leucine content in whole body proteins of 590 μmol/g protein.[31,32] Leucine oxidation was determined from the total CO_2 production rate, the $^{13}CO_2$ enrichment in the expired air, and the plasma 1-^{13}C-KIC enrichment, as described previously.[19,33]

Apparent nitrogen balances were calculated from the difference between the total intake and urinary output of nitrogen.

Evaluation of Data

The energy expenditure of the patients was evaluated by indirect calorimetry.[19] The daily expenditure was taken as the value obtained during the infusion period and extrapolated for the 24 h of the day. Paired t-tests were used to assess the differences in leucine kinetics and energy expenditure between the two dietary periods.

Results

Energy expenditure and the general clinical condition of the patients did not appear to differ significantly between the two dietary periods for each of these 12 patients. For the entire group, energy expenditure (mean ± SEM) was 32 ± 2.4 kcal × kg^{-1} × d^{-1}. This approximates 140% of the predicted basal metabolic rate (Table 4). In all cases energy expenditure was less than the energy provided by the enteral feeding. Therefore, the patients appeared to be in apparent positive energy balance.

Plasma BCAA concentrations showed the anticipated increase when patients received the BCAA diet, as compared to those when they received the egg protein diet (Fig. 4).

Leucine kinetics were examined in all 12 patients while they were in the fed state (Table 5). To assess and compare the effect of the two nutritional support regimens, the following parameters were examined: (1) the difference between the rate of incorporation of leucine into proteins and the rate of appearance of leucine via protein breakdown for each dietary period; this difference is defined as leucine balance; (2) the difference between the leucine balances during the two dietary periods (*i.e.*, balance during the BCAA period minus that for the egg protein period).

TABLE 4. *Energy Expenditure of the Burn Patients*

Patient No.	Total Energy Expenditure (kcal kg^{-1} d^{-1}) EGG	BCAA	BMR (Estimated)
1	26.9	27.8	20.7
2	33.8	30.4	25.4
3	18.9	40.6	20.9
4	52.8	47.4	23.6
5	33.0	35.5	22.0
6	31.0	32.3	20.9
7	25.6	22.8	23.2
8	33.5	29.3	21.9
9	23.6	24.1	22.1
10	20.5	19.6	21.1
11	30.4	36.0	21.6
12	34.0	38.0	21.1
Mean	30.3	32.0	22.0
SEM	2.5	2.3	0.4

BMR = basal metabolic rates calculated from Altman et al.[45]

The present results failed to show any significant difference in leucine balance ($p > 0.1$ by paired t-test) between the two dietary periods. Furthermore, there were no significant differences in the rate of leucine incorporation into, or release from, proteins ($p > 0.05$, by paired

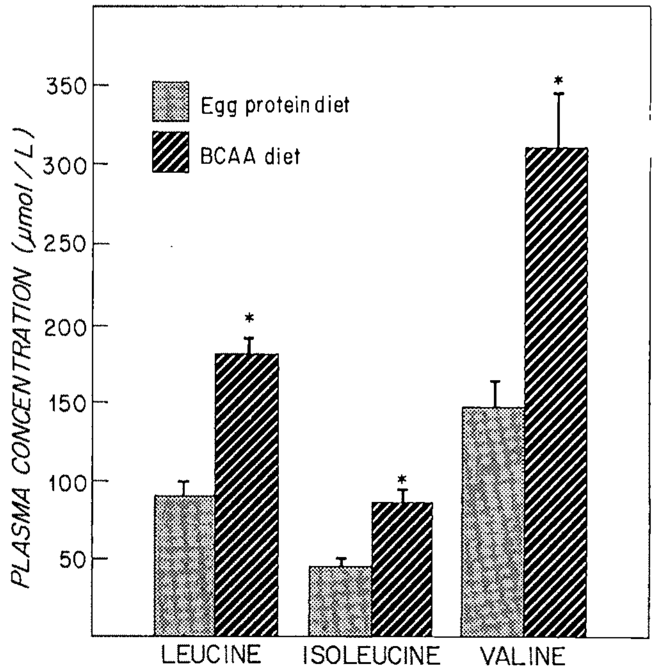

FIG. 4. Plasma BCAA concentrations in patients receiving the two diets. Levels of the BCAAs were significantly higher during BCAA feeding as compared to the egg protein period. *$p < 0.01$ by paired t-test.

TABLE 5. *Parameters of Leucine Kinetics in Burned Patients Receiving the Egg Protein and BCAA Diets*

Patient No.	Leucine Intake		Leucine Flux		Leucine Oxidation		Leucine to Protein (S)		Leucine from Protein Breakdown (B)		Leucine Balance (S − B)	
	Egg	BCAA	Egg	BCAA	Egg	BCAA	Egg	BCAA	Egg	BCAA	Egg	BCAA
1	44.3	96.0	297.9	218.2	45.1	52.0	252.7	167.2	253.5	122.3	−0.80	45.0
2	57.4	154.6	249.5	531.8	71.6	228.6	178.0	303.1	192.2	377.1	−14.2	−74.0
3	66.1	153.8	237.0	337.5	27.6	169.8	209.4	167.8	171.0	183.7	38.4	−15.9
4	61.6	133.6	351.8	530.7	105.2	224.5	246.6	306.4	290.2	397.3	−43.6	−90.9
5	33.8	82.8	177.9	204.8	41.0	101.6	136.9	103.2	144.1	122.0	−7.2	−18.8
6	52.5	122.0	155.8	325.3	20.7	150.0	135.1	175.3	103.3	203.3	31.7	−28.0
7	57.9	152.9	204.2	258.7	58.2	66.2	146.0	192.5	146.3	105.8	−0.3	86.7
8	36.9	79.9	208.4	243.9	48.7	78.3	159.7	165.6	171.5	164.0	−11.9	1.6
9	36.1	93.9	347.3	549.5	66.8	91.5	280.5	458.0	311.2	455.7	−30.7	2.2
10	37.4	91.9	169.6	219.5	25.2	72.7	144.4	146.9	132.2	127.6	12.2	19.3
11	37.2	86.0	129.7	198.5	25.3	85.6	104.5	112.8	92.5	112.5	12.0	0.3
12	42.8	92.5	142.5	184.8	47.3	88.9	95.2	95.9	99.7	92.3	−4.5	3.5
Mean	47.0	111.7*	222.6	316.9*	48.6	117.5*	174.1	199.6	175.6	205.3	−1.6	−5.8
SEM	3.0	7.9	20.2	37.4	6.5	16.2	16.0	28.1	19.5	34.2	6.0	12.6

All values are given as μmol × kg^{-1} × h^{-1}.

* Significantly different, $p < 0.01$ (by Student's t-test), from egg diet period.

t-test) between these two dietary periods (Table 5). However, the differences (either positive or negative) in leucine balance between the two dietary periods within individuals were negatively correlated with the differences in rates of release of leucine from protein breakdown ($r = 0.6$; $p < 0.05$).

BCAA feeding resulted in significantly ($p < 0.01$) higher levels of leucine flux and oxidation, as compared with the traditional egg protein formulation. From these results it appears that the major consequences of the increased intake of leucine was an enhanced rate of leucine oxidation.

Apparent nitrogen balance (Table 6) data in these 12 patients did not reveal any statistical difference between these two dietary periods ($p > 0.1$). In addition, urea and glucose kinetics (Table 7) failed to show significant differences between these two dietary periods ($p > 0.1$ paired t-test). Because the studies in the first seven patients did not show differences, we chose not to include an assessment of urea and glucose kinetics in the additional five patients. In accordance with these results, glucose and urea concentrations (Fig. 5) were similar between the two dietary periods.

From the present leucine kinetic data it can be estimated that the mean rates of whole body protein synthesis and breakdown were about to 7.1 g protein kg^{-1} d^{-1} for the egg protein period and about 8.4 g kg^{-1} d^{-1} for the BCAA period. These values are approximately double those reported for healthy young adults,[28,33,34] confirming that the rate of body protein turnover is substantially increased in severely burned patients.[19,34]

TABLE 6. *Apparent Nitrogen Balance in Burn Patients Receiving the Egg Protein and BCCA Diets*

Patient	Egg Protein (E)	BCAA (B)	Difference (B − E)
1	84.7	119.5	34.8
2	115.1	166.4	51.3
3	34.0	22.0	−12.0
4	−108.0	−214.0	−106.0
5	− 83.2	20.4	103.6
6	128.2	55.6	−72.6
7	19.3	27.0	7.7
8	−16.1	−81.2	−65.1
9	90.5	46.8	−43.7
10	85.0	105.0	20.0
11	58.3	12.4	−45.9
12	23.1	−16.9	−40.0
Mean	35.9	21.9	−14.0
SEM	±19.8	±26.2	±15.9

Values are given as mg N kg^{-1} d^{-1}.

TABLE 7. *Glucose and Urea Kinetics in Burned Patients Receiving the Egg and BCAA Diets*

Patient No.	Glucose Flux		Urea Flux	
	Egg	BCAA	Egg	BCAA
1	2551	3114	454	449
2	2479	2734	355	325
3	2280	2199	264	384
4	3805	2265	735	513
5	3116	2300	182	159
6	2248	2022	705	504
7	2096	1831	—	—
Mean	2654	2352	449	389
SEM	445	335	93	55

Values are given as μmol kg^{-1} h^{-1}.

Discussion

The present experiment was conducted in 12 severely burned nonseptic patients using a cross-over design in which each patient served as his or her own control in order to compare the metabolic responses to the two enteral formulations. A cross-over design was used to help minimize complications introduced by significant variations in the clinical and metabolic condition between patients and within each trauma patient over time.

Additionally, we used a relatively brief experimental dietary period, lasting 48–96 hours, and the order of the two periods was randomized. Clinical records revealed that for each patient there was little apparent difference in their condition between the two dietary periods, and this should permit a closer evaluation of the two enteral formulations. Of course, the brief length of the experimental study periods might be regarded as a limitation, but longer periods would introduce further problems for experimental design and interpretation.

It should be noted that the present study compared leucine kinetics and nitrogen balance in patients receiving two different formulas; these were not identical in all respects other than for the differences in BCAA levels. Thus, in one, an intact protein was the source of nitrogen and indispensable amino acids and in the other, it was a mixture of L-amino acids enriched with BCAA. Our choice of comparing these formulations was because it was important to use in one case a formulation routinely used in our clinical unit so that a potentially practical comparison could be then made with an amino acid mixture enriched with BCAAs. This latter formulation has been considered by some investigators[5–8,35] to offer possible advantages over conventional therapies for supporting protein metabolism in severely ill or catabolic patients, although no studies have made comparisons directly with conventional nutritional treatments. Clearly, it is possible that different results might have been obtained in our study if both of the formulations had been based on L-amino acid mixtures. Therefore, the present results should be considered in this context.

Some *in vitro* studies using incubated muscle preparations have revealed that higher concentrations of BCAAs in the incubation medium stimulate protein synthesis and decrease protein breakdown.[9,10] From such observations it has been hypothesized that a beneficial effect of leucine supplementation might be obtained in trauma patients. However, our *in vivo* leucine kinetic data fail to support this hypothesis. The present study demonstrated that a BCAA-enriched diet does not significantly alter the rate of leucine incorporation into, or release from, protein and, furthermore, that there was no measurable improvement in net body protein balance.

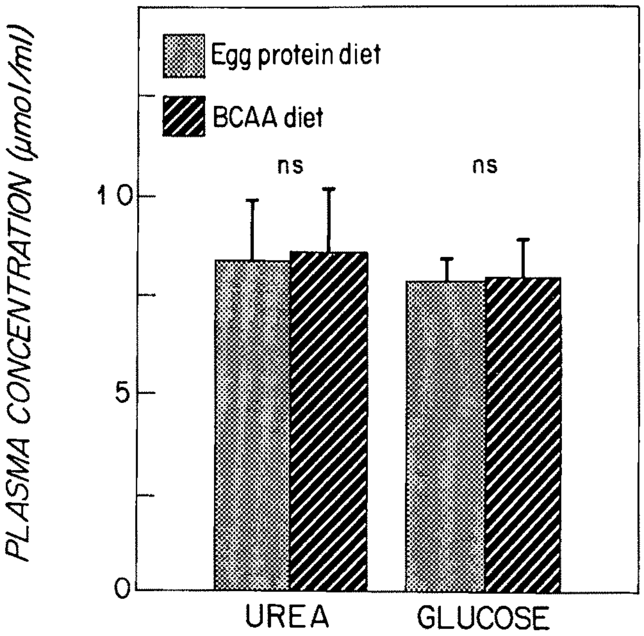

FIG. 5. Plasma glucose and urea concentration in patients during the egg protein and BCAA diet periods.

Previous studies have reported a significantly increased rate of plasma leucine disappearance and peripheral uptake rate of an exogenously infused leucine load in injured patients.[14–16] Because leucine and other BCAAs are oxidized to a significant extent in muscle, these earlier findings have been interpreted as reflecting an increased oxidation of BCAAs following trauma.[14–16] In combination with other findings, which show an impaired utilization of carbohydrates and fat as energy sources in trauma patients,[4,5,36] it has been proposed that BCAAs are consumed as a substitute fuel[5,11] and that this creates a deficit of BCAA availability for protein synthesis. With the aid of a leucine tracer, we have examined in the present study the metabolic fate of leucine in burn patients when given two different levels of BCAA support. It was possible, therefore, to evaluate the merits of this *BCAA deficit* hypothesis. Because rates of protein synthesis and breakdown both were found to be higher than for healthy, normal subjects, it is difficult to see that a deficit in the supply of leucine could be responsible primarily for the changes in amino acid and protein metabolism following burn injury.

Our investigation has further demonstrated that an enriched supply of BCAAs to burn patients does not significantly enhance the rate of leucine incorporation into proteins. Hence, we are unable to offer any evidence in favor of the hypothesis that the availability of BCAA is a rate-limiting factor for protein synthesis in burn patients. In parallel with these *in vivo* findings, there are reports[37–39] showing that the intracellular

BCAA concentrations in muscle are significantly elevated, rather than being depressed, in trauma patients. This may be a consequence of changes in leucine transport mechanisms or increased tissue proteolysis in response to trauma. Nevertheless, it would appear that a depletion of the intracellular free leucine pool is not a primary factor responsible for a reduced muscle protein balance under these conditions.

In addition, it has been proposed that BCAAs could substitute for other fuels in trauma patients and that a nitrogen-sparing effect[6,7,40] would be achieved by supplying higher than usual intakes of BCAA. Again, the results from the present study do not support this contention. Although we found that the rate of leucine oxidation was about double that with the BCAA diet, in comparison to the egg diet, this increase was not accompanied by any significant reductions in glucose flux or urea production. Clearly, the increased BCAA intake did not measurably influence the rate of glucose utilization, nor did it appear to spare body nitrogen loss by inhibiting proteolysis or improving nitrogen retention. Others have found that total BCAA oxidation accounts for about 2–5% of total energy expenditure.[41,42] Hence, the observed increase in leucine oxidation caused by BCAA feeding in the present study could only account for, at most, 4–10% of total energy expenditure for these patients.

Finally, it has been suggested that BCAA-enriched nutritional support may be of greater benefit in more severe cases of trauma. From our findings, it is difficult for us to offer support for this view. In the present study, differences in leucine balance between the BCAA and egg protein diets were not well correlated with the total burn area, the catabolic index[43] (data not shown), the nitrogen balance, or the leucine balance *per se*.

In summary, the present findings failed to show that a BCAA-enriched enteral feeding brings about additional metabolic benefits over those obtained with a more conventional, balanced, egg protein feeding. Thus, the BCAA treatment did not reveal consistent effects on protein synthesis or protein breakdown, as judged from the data on leucine kinetics. Indeed, protein synthesis rates in burn patients were high, irrespective of the nitrogen source of the feeding. Therefore, there is little reason to accept the idea that a primary deficency in the availability of BCAAs is responsible for the catabolic state of nitrogen metabolism under these conditions. Our conclusions are consistent with the findings of Milliken et al.,[18] who explored the effects of BCAA-enriched formulas in patients with cirrhosis. These investigators found with these formulas that there was an increased rate of leucine oxidation without an improvement in protein synthesis. Furthermore, Brennan et al.[44] have concluded, based on a the proceedings of a workshop concerned with BCAA supplementation in the nutritional therapy of hospitalized patients, that greater benefits must be demonstrated in man before any widespread application of the use of BCAA formulations can be recommended.

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The Relationship Between Primary Hyperparathyroidism and Diabetes Mellitus

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Previous reports have suggested that control of diabetes improves after successful parathyroidectomy for primary hyperparathyroidism. To investigate this proposition further, a review was made of all insulin-requiring diabetics undergoing curative parathyroidectomy at the Mayo Clinic between 1970 and 1984 (36 patients). All contemporary insulin-requiring diabetics undergoing thyroidectomy for benign euthyroid disease served as a control group (34 patients). One patient in each group had type I diabetes mellitus, and the remainder had type II diabetes mellitus. Preoperative insulin requirements, insulin requirements at follow-up, and change in insulin requirements did not differ significantly between the two groups. This study suggests that parathyroidectomy does not lead to a statistically significant reduction in the insulin requirements of diabetic patients with primary hyperparathyroidism and that coexistent type II diabetes mellitus should not be considered a further indication for parathyroidectomy in patients with primary hyperparathyroidism.

PREVIOUS REPORTS have suggested that control of diabetes improves after parathyroidectomy for hyperparathyroidism.[1-3] These reports have included patients with both primary and secondary hyperparathyroidism and both insulin-requiring and non-insulin-dependent diabetics. The total number of patients reported in these series who demonstrated decreased insulin requirements after parathyroidectomy was small, and no reports have used control groups. To clarify the effect of parathyroidectomy on glycemic control in diabetic patients with primary hyperparathyroidism, we compared preoperative and postoperative insulin dosages in two contemporary groups of insulin-requiring diabetics. One group underwent parathyroidectomy for primary hyperparathyroidism, and a control group underwent thyroidectomy for benign euthyroid disease.

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Patients and Methods

All insulin-requiring diabetics undergoing either curative parathyroidectomy for primary hyperparathyroidism or thyroidectomy for benign euthyroid disease between 1970 and 1984 were identified through a computer-based indexing system. Of the 70 patients identified, 36 had primary hyperparathyroidism and underwent parathyroidectomy (for adenoma in 32 and for hyperplasia in four), and 34 had benign euthyroid disease and underwent partial thyroidectomy (for multinodular goiter in 21 and for single or multiple thyroid adenomas in 13). All patients undergoing thyroid resection had normal preoperative total thyroxine levels, and none had a history of hyperthyroidism. Preoperative calcium values were normal in all patients undergoing thyroid resection, and no thyroid resection was associated with more than a minimal transient decrease in the postoperative serum calcium level. Review of pathology reports confirmed that all thyroid resections were performed without inadvertent excision of parathyroid tissue.

Patient records were reviewed to determine the age at onset, duration of diabetes, presence of a history of ketoacidosis, duration of insulin therapy, preoperative insulin dose, and preoperative weight. Instances of postoperative hypoglycemia, defined as any blood glucose determination of less than 40 mg/dL obtained within 5 days of operation, were recorded. Because all the patients were evaluated by staff endocrinologists before hospital admission, the appropriateness of their insulin therapy was ensured. Follow-up insulin doses and weights were obtained through review of the record or through con-

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TABLE 1. *Clinical Data from 70 Patients with Diabetes Mellitus, by Type of Disease*

Factor	Thyroid Disease Hyperparathyroidism	 Benign Euthyroid	P Value
No. of patients			
Male	12	10	0.72
Female	24	24	
Mean age (yr)	60.5	61.1	0.86
Mean duration of diabetes mellitus (mo)	152	142	0.78
Mean duration of insulin therapy (mo)	90	87	0.38

tact with the patient or referring physician. Comparisons between the two groups were made with either chi square analysis or Fisher's exact test for discrete variables and with Student's t-tests and Wilcoxon rank-sum tests for continuous variables.

Results

The parathyroidectomy group consisted of 12 men (33%) and 24 women (67%), and the thyroidectomy group consisted of 10 men (29%) and 24 women (71%) (p = 0.72). The mean age of the patients was 60.5 years in the parathyroidectomy group and 61.1 years in the thyroidectomy group (p = 0.86). The duration of diabetes was similar in the two groups (152 months in the parathyroidectomy group and 142 months in the thyroidectomy group, p = 0.78); the duration of insulin therapy was also similar (90 months and 87 months, respectively, p = 0.38) (Table 1). Both groups included one patient with juvenile-onset diabetes mellitus; both of these patients had histories of ketoacidosis (type I diabetes mellitus). All other patients had adult-onset diabetes mellitus without a history of ketoacidosis (type II diabetes mellitus).

Follow-up insulin doses were determined for 32 (89%) of the 36 patients in the parathyroidectomy group, and the average duration of follow-up in this group was 6.0 years (range: 2 months to 13 years); follow-up doses were determined for 28 (82%) of the 34 patients in the thyroidectomy group, and the average duration of follow-up was 7.8 years (range: 1–16 years). Four patients in the parathyroidectomy group and six patients in the thyroidectomy group were lost to follow-up. No correlation was noted between change in the insulin dose and duration of follow-up (Fig. 1). Weight at follow-up was obtained in 30 (83%) of the patients in the parathyroidectomy group and 27 (79%) of the patients in the thyroidectomy group, and the average durations of follow-up were 5.8 years and 8.2 years, respectively. No correlation was noted between change in weight and duration of follow-up (Fig. 2).

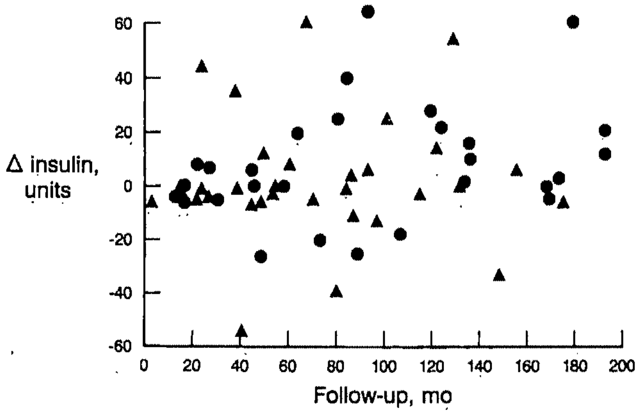

FIG. 1. Relationship of change in insulin dose and duration of follow-up in diabetic patients after parathyroidectomy (▲) and after thyroidectomy (●).

The mean insulin doses preoperatively and at follow-up were 37.2 units and 39.2 units/24 hours, respectively, for the parathyroidectomy group; the mean change in insulin dose was +2.1 units (SD: 23.2 units). Corresponding doses for the thyroidectomy group were 35.0 units and 43.1 units/24 hours; the mean change in dose was +9.6 units (SD: 22.6 units). Differences between the two groups were not statistically significant with respect to insulin dose preoperatively (p = 0.99) or at follow-up (p = 0.40). On average, 24-hour insulin doses increased by 7.5 units more in the thyroidectomy group than in the parathyroidectomy group (9.6 units *vs.* 2.1 units). This difference was not statistically significant (p = 0.21) (Table 2). At one extreme, the 95% confidence interval for this difference includes a mean increase in insulin dose of 19.5 units more for the thyroidectomy group than for the parathyroidectomy group. At the other extreme, the mean increase in insulin dose for the thyroidectomy group was 4.5 units less than that for the parathyroidectomy group. Figures 3 and 4 demonstrate the changes in insulin dose for patients in each group.

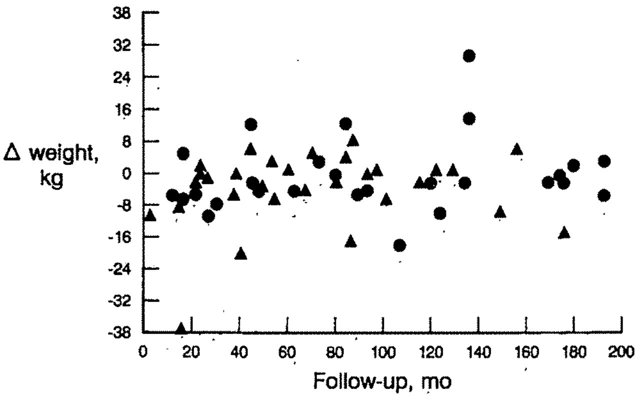

FIG. 2. Relationship of change in body weight and duration of follow-up in diabetic patients after parathyroidectomy (▲) and after thyroidectomy (●).

TABLE 2. *Insulin Dosages in 70 Patients with Diabetes Mellitus, by Type of Disease*

Time of Determination	Hyperparathyroidism		Benign Euthyroid Disease		P Value
	No. of Patients	Mean Dose (units/24 h)	No. of Patients	Mean Dose (units/24 h)	
Preoperatively	36	37.2	34	35.0	0.99
At follow-up	32	39.2	28	43.1	0.40
Change	32	+2.1	28	+9.6	0.21

Of the two patients with type I diabetes mellitus, the patient in the parathyroidectomy group experienced a decrease in insulin requirement of 3 units/day, and the patient in the thyroidectomy group experienced a decrease of 6 units/day.

The mean body weights preoperatively and at follow-up were 72.9 kg and 68.5 kg, respectively, for the parathyroidectomy group; the mean change in body weight was −3.4 kg. Corresponding weights for the thyroidectomy group were 73.5 kg, 72.1 kg, and −0.2 kg. The differences between the two groups were not statistically significant with respect to preoperative weight (p = 0.37), weight at follow-up (p = 0.32), or change in weight (p = 0.19) (Table 3).

Postoperative hypoglycemia occurred in one patient in the parathyroidectomy group but in none of the patients in the thyroidectomy group. Of those patients who had follow-up data, two (6%) in the parathyroidectomy group and one (4%) in the thyroidectomy group no longer required the administration of insulin.

Discussion

Several authors have noted an increased prevalence of diabetes among patients with hyperparathyroidism relative to that in the general population.[3–5] As pointed out by Ljunghall et al.,[4] this apparently increased prevalence may simply reflect a Berkson bias (*i.e.*, patients with diabetes are more likely to undergo routine biochemical testing than the general population and, thus, they are more likely to be found to have asymptomatic primary hyperparathyroidism).

Several reports have documented increased insulin secretion in response to glucose in patients with hyperparathyroidism.[4,6,7] In a study of nondiabetic patients with primary hyperparathyroidism, Ljunghall et al.[4] demonstrated that this response was diminished after parathyroidectomy. This decreased insulin response could be expected to be associated with a deterioration of glucose tolerance, and some deterioration was in fact found by Ljunghall et al.; however, this was not associated with a change in fasting glucose or hemoglobin A_{1c} levels. Similarly, no improvement was found in the control of diabetes in 36 patients (six requiring insulin) undergoing parathyroidectomy for primary hyperparathyroidism.[4]

Other reports have presented data suggesting that treatment of primary hyperparathyroidism may lead to improved control of diabetes. The reports by Walsh et al.[1] and Akgun and Ertel[2] each include one diabetic patient whose insulin requirement decreased after parathyroidectomy. A second patient reported by Akgun and Ertel[2] demonstrated improvement of an initially impaired glucose tolerance. Encouraged by these case reports, Cheung et al.[3] reviewed their experience with diabetic patients undergoing parathyroidectomy and classified them according to the criteria of the National Diabetes Data Group.[8] Of five patients with type I diabetes, two of the four with secondary hyperparathyroid-

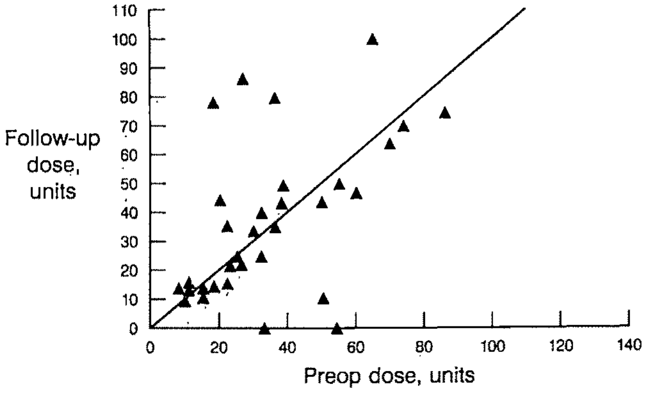

FIG. 3. Relationship of insulin dose at follow-up and preoperative insulin dose for diabetic patients undergoing parathyroidectomy. Straight line represents points of no change.

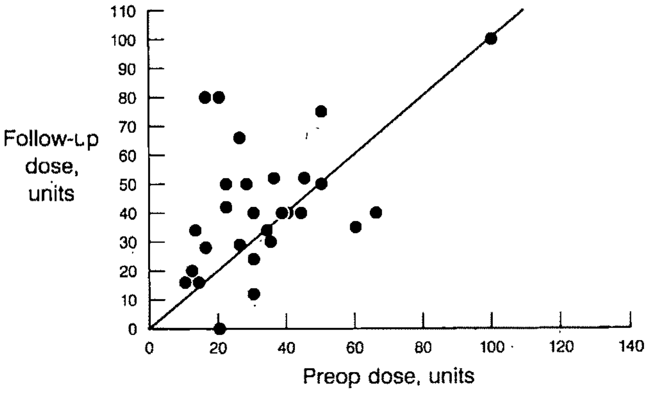

FIG. 4. Relationship of insulin dose at follow-up and preoperative insulin dose for diabetic patients undergoing thyroidectomy. Straight line represents points of no change.

TABLE 3. *Body Weight in 70 Patients with Diabetes Mellitus, by Type of Disease*

	Hyperparathyroidism		Benign Euthyroid Disease		
Time of Determination	No. of Patients	Mean Weight (kg)	No. of Patients	Mean Weight (kg)	P Value
Preoperatively	36	72.9	34	73.5	0.37
At follow-up	30	68.5	26	72.1	0.32
Change	30	−3.4	26	−0.2	0.19

ism and the one patient with primary hyperparathyroidism had decreased insulin requirements after parathyroidectomy. All patients with type II diabetes mellitus described by Cheung et al.[3] had primary hyperparathyroidism. At follow-up of 12 insulin-requiring diabetics with non-insulin-dependent diabetes mellitus, six demonstrated a decreased insulin requirement after parathyroidectomy, five had an increased requirement, and one had no change. Of their patients treated with oral hypoglycemic agents, three improved, nine remained stable, and three eventually required insulin. As they stand, these data do not suggest that parathyroidectomy alters the course of diabetes mellitus. However, Cheung et al.[3] pointed out that 27% of their patients did improve. They suggested that improvement in such a percentage is in marked contrast to the natural history of diabetes mellitus.[3]

By comparing the course of a group of diabetics undergoing parathyroidectomy with that of an appropriate control group, we hope to shed further light on the issue. In this retrospective review, we presented a series of consecutive insulin-requiring diabetics who underwent parathyroidectomy for primary hyperparathyroidism. We also presented a control group comprised of a contemporary series of consecutive insulin-requiring diabetics undergoing thyroidectomy for benign euthyroid disease. The two groups were similar with respect to age and sex distribution, duration of diabetes mellitus, and duration of insulin therapy.

On average, insulin dosages increased in both groups from the preoperative state to follow-up. The increase in insulin dosage was of a lesser magnitude for patients undergoing parathyroidectomy than for those undergoing thyroidectomy. However, the difference (an increase of 7.5 units more for the thyroidectomy group) was not statistically significant. At least 100 patients would be required in each group to identify the significance of this difference with 80% confidence. Our data allow us to state with 95% confidence that any relative decrease in insulin requirement incurred by parathyroidectomy would be less than 19.5 units/24 hours at approximately 6 years of follow-up. Also, our data do not exclude the possibility that parathyroidectomy may even be associated with a slight relative increase in insulin requirements. Note that only two patients in the parathyroidectomy group (and one in the thyroidectomy group) were rendered free of exogenous insulin at follow-up. It thus seems unlikely that parathyroidectomy is associated with dramatic changes in the insulin requirements of diabetics with primary hyperparathyroidism.

A decrease in insulin requirements induced by parathyroidectomy could have been masked by a disproportionate gain in body weight by the parathyroidectomy group. However, the two groups did not differ significantly in regard to preoperative body weight, body weight at follow-up, or change in body weight. Although previous reports have cautioned that diabetic patients with primary hyperparathyroidism undergoing parathyroidectomy may be particularly prone to postoperative hypoglycemia,[2,3] we found this complication in only one of 36 patients.

We were unable to demonstrate that parathyroidectomy leads to a significant reduction in insulin requirements of type II diabetics with primary hyperparathyroidism. Our data do not allow us to reach a conclusion regarding type I diabetics. However, on the basis of existing data, coexistent type II diabetes mellitus should not be considered a further indication for parathyroidectomy in patients with primary hyperparathyroidism.

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Assessment of the Use of Transfusion Therapy Perioperatively in Patients with Sickle Cell Hemoglobinopathies

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During the period of 1978 to 1986, 66 patients (31 men, 35 women) with a mean age of 28.4 years and various sickle cell hemoglobinopathies underwent 82 surgical procedures; 28 were emergencies. Fifty of the 66 patients had HbSS, 13/66 had HbSC, and 3/66 had HbS-thalassemia. All 66 patients received transfusions, although not for all procedures. In 48 patients, transfusion therapy was only administered preoperatively. Simple transfusions (1 to 10 units) were administered in 31 of 48 procedures. Exchange transfusions (1 to 6 units) were performed in nine of 48 procedures. Preoperative hematocrit ranged from 7.0% to 54.2%; of those receiving transfusions the hematocrit ranged from 22.6% to 53.7%. Intraoperative transfusions (1 to 10 units) were performed in 14 of 82 procedures; postoperative transfusions (1 to 6 units) were performed in 13 of 82 procedures. No advantage was noted in preoperative exchange transfusion as measured by a decrease in postoperative complications; a slight increase was seen in atelectasis in this group of patients with preoperative transfusions. An increase was reported in the complication rate of patients with an hematocrit of <30%. The type of transfusion (preoperative, intraoperative, or postoperative) administered did not appear to be related to postoperative morbidity rates. The complication rate for simple transfusions was 51.6% and for multiple transfusions, 55.6%. HbSS hemoglobinopathy had the higher complication rate. The hepatitis B surface antigen was demonstrated in four of 66 (6.1%) patients; ten of 66 (15.2%) developed alloantibodies. The benefits of transfusion therapy should be judged according to clinical needs; not all sickle cell patients need exchange or preoperative transfusion.

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THE USE of blood transfusion therapy in patients with sickle cell hemoglobinopathies either before or after surgery remains a controversial issue. Sickle cell anemia patients are regarded as being at increased risk for surgery. Slight decreases in pH, partial pressure of oxygen (PO_2), blood flow, blood volume, and temperature that occur during surgery may cause a distortion of the biconcavity of these patients' red blood cells into an elongated sickle cell because of the high content of hemoglobin S (HbS).[1] A reduction of blood flow within the capillaries occurs, resulting in further deoxygenation and lowering of the pH. This may eventually lead to a vaso-occlusive crisis with ischemic infarction of the involved tissues resulting in abdominal and skeletal pain, splenic infarction in young children, necrosis of bone marrow, pulmonary infarction, cerebral infarction, hematuria, priapism, or hemolysis.[1] Thus, adequate hydration and oxygenation, as well as avoidance of acidosis and prolonged blood stasis, are thought to be mandatory in the preoperative management of sickle cell anemia patients.

Many authors[2-10] believe that adequate preoperative preparation also requires transfusion therapy to reduce the relative amount of HbS available for sickling and increase the oxygen-carrying capacity of the blood. Janik and Seeler[10] have demonstrated the safety with which such procedures can be performed. In their study, 35 children with HbSS, HbSC, or HbS-thalassemia disease underwent 46 operations without significant mortality rates after having received preoperative transfusion therapy.

Nevertheless, many researchers[11] believe that careful attention to preoperative management and anesthetic

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technique may be more important than any type of transfusion therapy in sickle cell patients. Some reports[12] state that preoperative transfusion therapy has been associated with a higher postoperative complication rate than in patients not receiving transfusions. The purpose of this study was to review the perioperative experience with sickle cell patients and evaluate elective transfusion therapy over standard care.

Materials and Methods

Between March 1978 and March 1986, 66 Black patients with various sickle cell hemoglobinopathies underwent a total of 82 surgical procedures at the Tulane Medical Center Hospital and Charity Hospital of Louisiana at New Orleans (Table 1). Twenty-eight of these procedures were emergencies and the remaining 54 were elective. Fifty of the 66 patients had HbSS, 13 of 66 had HbSC, and three of 66 had HbS-thalassemia. The patient ages ranged from 1 to 44 years (mean: 28.4 years), and hospital stay ranged from 2 to 44 days (mean: 23.6 days). Of the 66 patients in this study, 31 were men and 35 were women. Preoperative transfusion therapy (either single or exchange) was performed in all 66 of the patients, although not in all procedures. In only 48 patients, transfusion was given preoperatively and at no other time. Simple transfusions were administered in 31 of 48 procedures, with the amount of blood given ranging from 1 to 10 units. Exchange transfusions (ranging from 1 to 6 units) were performed in nine of 48 procedures, and both simple and exchange were performed in the remaining eight. Preoperative hematocrits upon admission ranged from 7.0% to 54.2%, and the hematocrits in those receiving transfusions before surgery ranged from 22.6% to 53.7%. A preoperative hematocrit of at least 36.0% occurred in 15 of the procedures.

No transfusions were given preoperatively in 16 of the procedures. Five of the 16 patients eventually received either an intraoperative or postoperative transfusion, but the remaining 11 patients did not receive a transfusion at any time during their hospital stay. The patient charts indicate that in all 11 of the procedures the patients received the standard preoperative care given to those with sickle cell hemoglobinopathies. They were adequately supported with intravenous (I.V.) fluids and were kept well-oxygenated both preoperatively and intraoperatively. Body temperature preoperatively was maintained at a level of 35.8 C to 38.0 C. No statistical difference was noted, however, in the amount of standard preoperative care received by the group that received transfusions and the group that did not.

The types of anesthesia administered varied and consisted of such agents as halothane, sublimaze, epidural (marcaine), ethrane, nitrous oxide, fentanyl, forane, pentathane, and local (xylocaine).

TABLE 1. *Surgical Procedures in Sickle Cell Patients, 1978–1986*

Surgical Procedures	Elective	Emergency
Umbilical herniorrhaphy	5	0
Cholecystectomy	11	9
Dilation and curretage	3	3
Tubal ligation	6	0
Hysterectomy	2	0
Skin flap	3	0
Splenectomy	3	5
Tonsillectomy	6	0
Appendectomy	0	3
Open reduction and internal fixation of hip and ankle	0	2
Mastectomy	1	0
Penile revascularization	9	0
Cesarean section	2	3
Vitrectomy	0	2
Cervical lymph node biopsy	1	0
Arteriovenous fistula repair	1	0
Exploratory laparotomy (left ovarian vein thrombosis)	0	1
Warren shunt	1	0
Totals	54	28

Intraoperative transfusions (ranging from 1 to 10 units) were performed in 14 of 82 surgical procedures. Three of the 14 patients were administered blood intraoperatively only. Postanesthesia recovery consisted of maintaining adequate hydration and body temperature. Most patients received short-term oxygen therapy in the immediate postoperative period. Postoperative transfusions (ranging from 1 to 6 units) were performed in 13 of 82 procedures, with two of 13 receiving blood postoperatively only.

The following perioperative complications were evaluated in all 82 surgical procedures: transfusion reaction, fever (secondary to atelectasis, urinary tract infection, thrombophlebitis, wound infection, antibiotics, *etc.*), sickle cell pain and hemolytic crises, volume overload, dehydration, pulmonary embolism, and jaundice. Long-term complications reviewed were the development of hepatitis or alloantibodies.

Results

Table 2 shows the number of postoperative complications encountered in the following subsets: Group 1 included the patients who received only preoperative transfusion therapy (N = 48); Group 2 included those who received no transfusion therapy (N = 11); Group 3 consisted of those who received a preoperative transfusion plus either an intraoperative or postoperative transfusion (N = 18); and Group 4 consisted of those who received either an intraoperative or postoperative transfusion, but not a preoperative transfusion (N = 5). Log-linear analyses were used to determine the impact of transfusion therapy on the complication rate after

TABLE 2. *Postoperative Complications*

Complication	Group 1[*] (N = 48)[†]	Group 2 (N = 11)	Group 3 (N = 18)	Group 4 (N = 5)
Hypoxia	4	0	2	0
Acidosis	7	1	1	1
Hypothermia	10	1	2	0
Transfusion reaction	0	0	0	1
Fever				
Atelectasis	10	0	5	0
Urinary tract infection	1	0	1	0
Thrombophlebitis	0	0	1	0
Wound infection	1	0	1	0
Other[‡]	6	3	6	1
Pain crisis	3	0	3	0
Hemolytic crisis	1	1	3	0
Pulmonary embolism	0	0	2	0
Volume overload or dehydration	0	0	1	0
Jaundice	1	0	3	0
Hepatitis	2	0	2	0
Alloantibodies	6	1	4	0

[*] Group 1 = those receiving preoperative transfusions only. Group 2 = those receiving no transfusion. Group 3 = those receiving preoperative transfusion and either an intraoperative or postoperative transfusion. Group 4 = those receiving intraoperative or postoperative transfusion, but no preoperative transfusion.

[†] Number of procedures (total 82).

[‡] Includes patients with unexplained fever, upper respiratory tract infections, left lower lobe pneumonia, endometritis, and seizures.

controlling for other variables. In comparing the number of postoperative complications in Group 1 with Group 2, it can be seen by way of percentages that the patients in Group 1 fared no better than those in Group 2, and in some cases worse. In fact, a statistically significant difference ($p < 0.001$) was noted between the amount of postoperative atelectasis experienced by the patients in Group 1 and those in Group 2. It would appear that those receiving transfusion therapy were at a higher risk of developing postoperative atelectasis than those who received no transfusion therapy. Group 3 patients also appeared to have a high complication rate; however, when comparing the complication rate of all four groups, no statistically significant difference was found.

A relationship was found between the immediate preoperative hematocrit and postoperative complication rate. A statistically significant difference ($p < 0.08$) was noted in the complication rate experienced by the patients with a preoperative hematocrit of $<30.0\%$, those with a preoperative hematocrit of 30.0–35.9%, and those with a preoperative hematocrit of $>36.0\%$. Thus, it would appear that sickle cell patients entering surgery with a hematocrit of at least 36.0% have a lower incidence of morbidity than those under this level. The effect of the preoperative white blood cell (WBC) count on postoperative morbidity rate was also analyzed. Using 15.0 as a normal WBC count in sickle cell patients,[13] no significant difference was found in the complication rate between those with a preoperative WBC count of >15.0 and those with a WBC count of <15.0.

The type of transfusion administered did not appear to be related to postoperative morbidity rate. The complication rate in patients receiving simple transfusions was 51.6%, whereas those receiving exchange transfusions had a complication rate of 55.6%. No statistical difference was encountered in any of the postoperative complications between the patients who received simple and those who received exchange transfusions.

When the effect of the type of hemoglobinopathy on the postoperative complication rate was analyzed comparing the postoperative morbidity rate of those patients with HbSS *versus* those with either HbSC or HbS-thalassemia without taking transfusion therapy into account, it was found that the HbSS patients had a significantly higher ($p < 0.05$) complication rate. Of the HbSS patients who had a complication, however, 88% had also received a preoperative transfusion, whereas only 66.7% of those with HbSC or HbS-thalassemia who had also received transfusion had complications. Interestingly, nine of 11 patient-procedures who received no transfusion therapy were either HbSC or HbS-thalassemia. In this group of 11 patients, no difference was noted in the postoperative complication rate among the HbSS patients or those with HbSC or HbS-thalassemia.

The surgical procedures listed in Table 1 were classified as either emergency or elective. Without taking transfusion therapy into account, it was found that the postoperative complication rate for the patients undergoing elective or emergency surgery was similar. Including the administration of transfusions with this analysis, no relationship was found between the type of admission and postoperative morbidity rate. The hepatitis B surface antigen was identified in four of 66 patients, and ten of 66 patients developed alloantibodies.

Discussion

The perioperative morbidity and mortality rates in patients with major sickle cell hemoglobinopathies is known to be significant. Flye and Silver[7] reported a serious complication rate of approximately 50%, which included pneumonia, fever >103 F, and sickle cell crises. Ariyan et al.[6] found the collective postcholecystectomy morbidity rate to be 34%, with pulmonary complications being the most common. A study by Spiegelman and Warden[2] reported a 25% incidence of postoperative complications in 12 sickle cell children who underwent 29 surgical procedures. Three of the patients suffered from subsequent atelectasis and pneumonia: two with wound infections, one from a postoperative crisis, and one with a subhepatic hematoma.

As a result of these complications, strict perioperative management is thought to be essential in sickle cell patients. Sufficient preoperative hydration serves to decrease blood viscosity and microvascular sludging. Hypothermia can be avoided by keeping the patient under blankets throughout the perioperative period. The anesthesiologist must ensure proper oxygenation of the patient before induction of general anesthesia. Arterial blood gases should also be monitored because hypoxia and acidosis may precipitate vaso-occlusive crises. Holzmann et al.[3] concluded in their study that it was not the type of anesthetic agent used that was important, but the avoidance of hypoxemia, acidosis, hypotension, hypovolemia, and hypothermia that was critical.

Lessins et al.[14] showed that *in vitro* filterability of blood is almost normal when a cell mixture contains <40% sickle cells and clinically vaso-occlusive crises occur only when the level of HbS exceeds 50%. Hence, this is the rationale many researchers have been using for performing preoperative transfusion therapy in sickle cell patients. Janik and Seeler[10] stated that they propose a preoperative transfusion of 15–20 mL of packed erythrocytes per kilogram of body weight to a hematocrit of 36% in children with sickle cell hemoglobinopathies. Simple transfusions are advocated by almost all investigators when sickle cell patients have low hemoglobin levels preoperatively, and this technique has been successful in raising the hematocrit and HbA levels while at the same time diluting out the HbS. The oxygen-carrying capacity of the blood is increased as well. Such transfusions also suppress the generation of sickle cell by the bone marrow if performed several days before surgery.[15] The inherent disadvantages of this particular technique are the possibility of prolonged marrow suppression leading to an aplastic crisis and a theoretic increase in the blood viscosity that may precipitate a crisis.[15] Anderson et al.,[16] however, have shown that the addition of normal erythrocytes to sickle cells does not increase the viscosity, and may even decrease it. Simple transfusions may also impose volume overload and the risk of congestive heart failure.[17] Our data show that although there may be some benefit in raising a patient's hematocrit preoperatively, if it is excessively low, the risks of performing such a transfusion appear to outweigh the benefits in any other situation.

Lanzkowsky et al.[17] advocated volume exchange transfusion in preparing the patient for surgery. This technique involves transfusing 15 mL/kg of packed erythrocytes into an antecubital vein while simultaneously removing 20 mL/kg of whole blood by gravity from the opposite antecubital vein. They believe the advantages of this procedure include the rapid removal of sickle cells from the circulation, reduction of blood viscosity, no volume overload, and prevention of hemosiderosis resulting from repeated transfusions. They also believe exchange transfusions in refractory painful crises of sickle cell anemia assist in removing activated procoagulants, retard the formation of excessive thrombin, and thereby help restore normal circulation by decreasing relative resistance. The use of exchange transfusions has been shown to be clearly indicated in patients with sickle cell disease in cases of acute priapism, in the acute chest syndrome with hypoxia, in the scleral buckling procedure for retinal detachment, and before cardiopulmonary angiography (hypertonic dye may cause sudden localized retrovascular sickling).[18] It is also believed[19] that exchange transfusions in patients with overwhelming infection may provide immunologic components at the site of infection, remove bacteria and endotoxins, and improve splenic function by improving the microcirculation. This technique is time-consuming, and blood administration and withdrawal in the small child can be a difficult procedure. Although whole blood exchange transfusions have been shown to be effective by several other investigators,[20–23] our data indicate no advantage of exchange transfusions over single transfusions, or even over those patients who did not receive any transfusion therapy.

Some disadvantages of both simple and exchange transfusions inherent to transfusions themselves are hepatitis, transfusion reactions, development of atypical antibodies, and acquired immune deficiency syndrome (AIDS). Fullerton et al.[24] stated the risk of hepatitis is minimal. In their study group of 260 patients exposed to over 5000 transfusions, only one patient demonstrated a positive hepatitis B surface antigen and six were positive for HbS antibodies. Irregular alloantibodies were found in 7.9%, but only 1.8% had antibodies to more than one red cell antigen. Our study showed four of 66 (6.1%) patients demonstrated the hepatitis B surface antigen, whereas ten of 66 (15.2%) developed alloantibodies. No patient to date has developed AIDS. These data imply considerable risk-morbidity rates as a result of blood transfusions to the sickle cell patient.

Morrison et al.[25] stated that to lower the incidence of hepatitis even further, the donor blood should be proved to be Australia antigen negative and obtained from a family member or friend who has never had a history of liver diseases. The use of buffy coat poor washed red cells should reduce the incidence of reactions to white cell antigens, as well as dilute the hepatitis virus if present.

Curran et al.[26] provided substantial evidence that transfusion-related AIDS does occur. Although this is currently an extremely infrequent complication of blood transfusion, physicians must weigh the risk of transfusion against the expected benefit. Ellison and Ferrara[15] stated that in the absence of symptomatic anemia, the benefits of preoperative transfusions do not uniformly outweigh the risks outlined above. Our study supports this belief and it appears that the benefits of transfusion should be judged according to the clinical situation.

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Management of Severe Caustic Stenosis of the Hypopharynx and Esophagus by Ileocolic Transposition *Via* Suprahyoid or Transepiglottic Approach

Analysis of 18 Cases

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Eighteen cases of severe chronic caustic stenosis of the hypopharynx and esophagus are presented. Restoration of digestive continuity was accomplished by retrosternal ileocolic transposition. The cervical approach and the position of anastomosis depended on the status of the hypopharynx. When one pyriform sinus remained open (type I, N = 4), an anterior suprahyoid approach was used in conjunction with lateral hypopharyngotomy because it facilitated the anastomosis and additional minor surgical procedures. When the hypopharynx was completely stenosed (type II, N = 14), a transepiglottic approach consisting of partial horizontal laryngectomy was used because it allowed excision of the supraglottic stricture, restoration of the oropharyngeal cavity, anastomosis to the posterior oropharyngeal wall, management of an eventual laryngotracheal stenosis, and elevation of the laryngeal inlet above the digestive anastomosis. After operation, several endoscopic examinations were required, sometimes combined with reoperation. Return of deglutition assuring normal nutrition was obtained in 61% of patients: 3 of 4 type I and in 8 of 14 type II.

MASSIVE INGESTION of a corrosive agent usually results in a life-threatening clinical condition that requires emergency intensive care often combined with surgical intervention.[1–4] If the esophagus has been removed in the initial emergency or progressively stenosed as a result of the caustic burn,[5,6] reconstructive surgery is frequently required to restore digestive continuity. The concomitant development of severe hypopharyngeal stricture is an infrequent yet critical complication, occurring in one of 145 patients (0.7%) in the study of Cardona and Daly,[7] and in one of 16 patients (6%) in Schild's study.[8] As pointed out by Gupta,[9] such an association raises a major problem in that: (1) the upper anastomosis of the digestive graft used to bypass the stenotic area is located at the level of the laryngeal inlet, and (2) fibrosis of the pharyngeal wall affects its capacity to propel the bolus through the anastomosis in the first voluntary stage of deglutition. Thus, restoration of digestive continuity in this area interferes with the mechanisms of deglutition and respiration.

In the literature, some studies have described the epidemiologic[7,8,10] and endoscopic[8,10,11] aspects of such lesions and highlighted the controversies and difficulties in their medical[7,8,10,12] and surgical[13–18] management. The bypass procedure adopted have consisted of transposition of the stomach,[9,16] of the right[13,14,16,17] or transverse[13,14,17] colon, or of a free jejunum graft.[16] The pharynx was entered anteriorly,[13,14] laterally,[13–18] or posteriorly.[9,16] Resection of scar tissues was followed by Z-plasties[15,19] and/or covering the raw area with skin or dermal graft,[14,15] or local or regional mucosal or skin flaps.[17] However, the limited number of cases reported in most of these studies makes it difficult to evaluate and compare the functional benefit of the various procedures described.

At the Paris poison center between 1978 and 1986, 11 of 528 patients (2.1%) admitted for caustic ingestion burns developed combined hypopharyngoesophageal strictures requiring surgical treatment. Seven additional patients were referred from other centers for reconstruction. This paper: (1) reports the clinical features and results of these 18 cases; (2) describes the technique we have developed with special emphasis on the anterior cervical approach either suprahyoid or transepiglottic; and (3) emphasizes the role of the laryngologist, especially in the clinical assessment of the lesions and in postoperative management.

Patients and Methods

Table 1 summarizes the main clinical features of the 18 patients.

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TABLE 1. *Clinical Features of the 18 Patients*

Case No.	Sex, Age, Cause	Emergency Treatment	Year of Reconstruction	Type of Digestive Lesions, Associated Lesions	Delay	Approach of the Pharynx	Secondary Operations	Functional Results
1	M, 30 yrs, suicide	IC, jejunostomy, jejunostomy, tracheostomy	1978	II	2 yrs	Lateral pharyngotomy	Cervical enterotomy (×2)	Failure
2	F, 24 yrs, accident	IC, gastrostomy	1978	II, laryngotracheal stenosis	9 yrs	Transepiglottic	Cervical enterotomy	Satisfactory
3	F, 57 yrs, suicide	IC, tracheostomy	1979	I	6 mths	Lateral pharyngotomy + suprahyoid	Cervical enterotomy, new ileopharyngoplasty	Poor
4	M, 36 yrs, suicide	IC	1979	II	2 yrs	Lateral pharyngotomy	Pharyngoplasty with D.P. flap	Poor
5	F, 28 yrs, suicide	IC, surgery, tracheostomy	1979	II	4 mths	Lateral pharyngotomy	Pharyngoplasty with D.P. flap	Satisfactory
6	F, 48 yrs, accident	IC, gastrostomy	1980	I	28 yrs	Suprahyoid		Satisfactory
7	F, 44 yrs, suicide	IC, surgery	1980	I	5 mths	Suprahyoid	New ileopharyngoplasty	Satisfactory
8	F, 44 yrs, suicide	IC, surgery	1981	II	4 mths	Transepiglottic		Satisfactory
9	F, 58 yrs, suicide	IC	1982	I, laryngotracheal stenosis	5 mths	Suprahyoid	New ileopharyngoplasty	Satisfactory
10	M, 58 yrs, suicide	IC, surgery	1982	II	5 mths	Transepiglottic	Cervical enterotomy	Satisfactory
11	F, 25 yrs, suicide	IC	1982	II	6 mths	Transepiglottic		Satisfactory
12	M, 21 yrs, suicide	IC	1984	II	8 mths	Transepiglottic	Cervical enterotomy, new ileopharyngoplasty	Poor
13	F, 31 yrs, suicide	IC	1984	II	5 mths	Transepiglottic	New ileopharyngoplasty	Satisfactory
14	F, 19 yrs, suicide	IC, surgery, tracheostomy	1984	II, laryngotracheal stenosis	1 yr	Transepiglottic		Poor
15	F, 15 yrs, suicide	IC, surgery, tracheostomy	1985	II	4 mths	Transepiglottic		Satisfactory
16	M, 23 yrs, accident	IC, surgery, tracheostomy	1985	II	4 mths	Transepiglottic	Cervical enterotomy	Failure
17	F, 29 yrs, suicide	IC, surgery, tracheostomy	1986	II	7 mths	Transepiglottic	Cervical enterotomy	Satisfactory
18	F, 46 yrs, suicide	IC, surgery, tracheostomy	1986	II	9 mths	Transepiglottic	Excision of ileocolic graft	Failure

Age and Sex Distribution

Age ranged from 15 to 58 years with an average of 35 years. Five patients were men, 13 were women.

Causes and Ingested Products

In 16 cases, ingestion took place in suicide attempts. This occurred in two schizophrenic patients and in nine patients with depressive, compulsive, and aggressive personality patterns. In five cases, no psychological evaluation was made because of linguistic problems. In two cases, ingestion was accidental.

The responsible agents were always household products, sold in France, with no restriction and with insufficient instructions for use. In 17 of the 18 cases, it was a strong base, highly concentrated sodium hydroxide added to a nonionic surface-active agent, in liquid or crystal form. In one case, it was nitric acid. The approximate volume ingested ranged from 50 to 400 ml.

Initial Treatment

All patients were initially treated as severe burns in an intensive care unit. In 12 cases, emergency surgery was performed based on previously published criteria.[1,4] Surgery consisted of laparotomy and feeding jejunostomy or gastrostomy in three cases, and gastrectomy with transhiatal blunt esophagectomy by stripping, feeding lateral jejunostomy, and cervical esophagostomy[4] in nine cases. Two of these 9 patients had a tracheobronchial necrosis due to aspiration of the corrosive agent or to extension of the necrotic process from the esophagus to the trachea. This was treated by thoracotomy, patching of the back wall of the trachea with pulmonary apposition, and temporary tracheostomy. In four of the 12 surgical patients and in one nonsurgical patient, tracheostomy was also performed because of acute supraglottic edema. This tracheostomy was maintained until the time of reconstructive surgery.

Chronic Caustic Lesions

Corrosive injuries of the upper digestive tract and the classification adopted are described in detail in the section on endoscopic evaluation. In the 18 cases considered, chronic caustic lesions involved mild burns of the buccal or oropharyngeal cavity, major stenosis of the hypopharynx with supraglottic stricture and, in the nine cases without emergency esophagectomy, complete obliteration of the esophagus. According to our classification, four patients were considered type I, and 14 were considered type II.

They were three cases of major laryngotracheal lesions: (1) two cases of incomplete laryngotracheal stenosis that were treated by the standard laryngofissure procedure, 2 years before reconstructive surgery in one case and 1.5 years after surgery in the other case; (2) one complete stenosis of the larynx that required a total laryngectomy 2 years after the ingestion and 6 months before reconstructive surgery.

Delay between Ingestion and Reconstructive Surgery

The interval from caustic ingestion to reconstructive surgery ranged from 4 months to 28 years.

Types of Reconstructive Surgery

In all instances, re-establishment of digestive continuity was achieved by retrosternal transposition of the right ileocolon, except in one case where the transverse colon was used. The oropharyngeal approach was accomplished by: (1) lateral pharyngotomy in four cases; (2) anterior suprahyoid pharyngotomy in four cases; (3) anterior epiglottectomy (transepiglottic approach) in 11 cases.

Intra- and Postoperative Complications

Necrosis of the ileocolon occurred at the 13th postoperative day in one patient requiring emergency excision of the digestive graft. Four pneumothoraces occurred during construction of retrosternal tunnels. They were complicated by empyema in two cases, but all resolved without sequelae. Four cervical and one abdominal fistulae occurred at the level of the digestive anastomosis and healed in a few days. One case of phlebitis of the left arm resolved with treatment. There was no surgical mortality.

Results

The first postoperative endoscopy was performed between weeks 1 and 2 after surgery. In two cases, the site of anastomosis could not be found, probably because of the extreme evolutivity of the stenotic process. In these two cases, new operations were performed a few months later but the final results were failures. In one other case, necrosis of the ileum was observed which required immediate excision of the graft. No further attempt at reconstruction was made. In the 15 remaining cases, endoscopic sessions were performed each week during the first month, every 2–3 weeks the following months, and then as needed. In 10 of these 15 cases, one or several operations were required. They consisted of retrograde digital dilation by cervical enterotomy in 6 cases, new ileopharyngoplasty in five cases, and new pharyngoplasty by means of a deltopectoral flap in two cases.

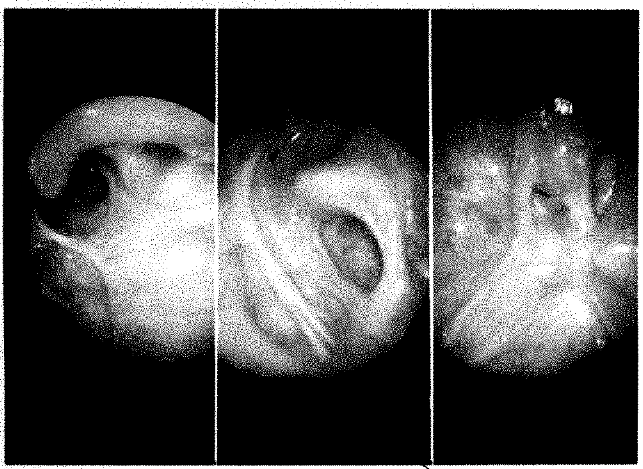
From a functional point of view, results were not assessed before the 6th postoperative month. The criteria of success were exclusive oral alimentation of both liquids and solids, stable body weight, no more than two endoscopic dilations per year, and good phonatory function. Accordingly, our results can be analysed as follows: (1) three cases were failures, in one case because of necrosis of the ileocolic graft and in two cases because of persistent restricturing of the corrosive lesions. Despite new operations, patent anastomoses could not be obtained. Moreover, these two highly disturbed patients refused any care, including attempting to smallow, and died of severe malnutrition. (2) In four cases, results were poor. Despite repeated endocopic dilations and/or repeat surgery, severe dysphagia persisted. These patients continue to be fed by jejunostomy and still have tracheostomy. (3) The 11 remaining patients had satisfactory results with follow-up ranging from 1.5 to 8 years. This was obtained without further endoscopic dilation in two cases, with one or two endoscopic dilations per year in three cases, and with reoperation followed by annual or biannual endoscopic dilations in six cases. Barrium swallow x-ray studies confirmed the subjective appraisal of deglutition.

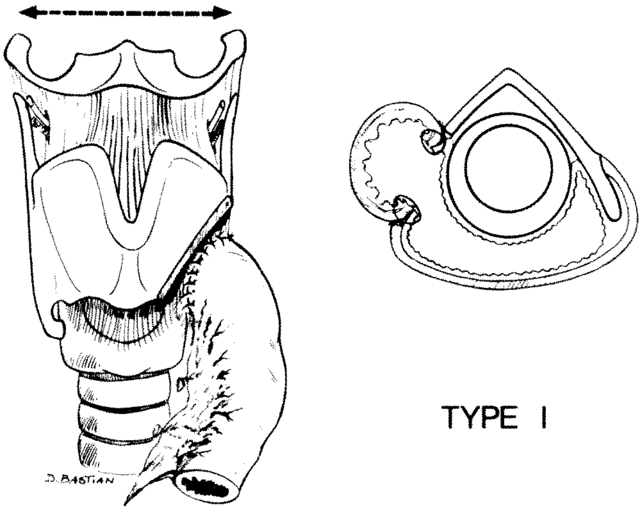
Thus, functional results were satisfactory in three of four type I lesions, and in eight of 14 type II lesions.

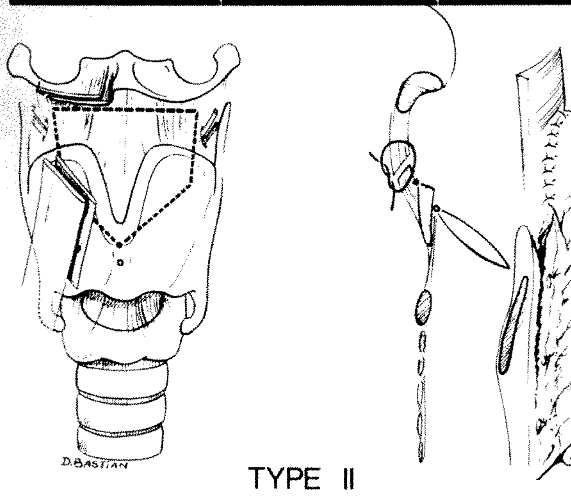
Discussion

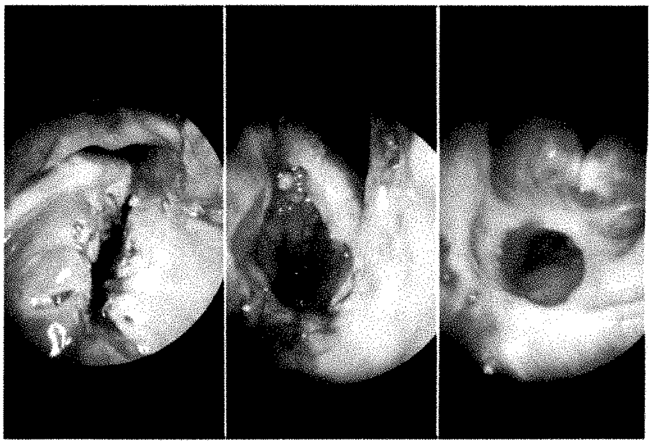
The main surgical problem raised by the combined hypopharyngeal and esophageal stenosis is that restoration of digestive continuity interferes with the processes of deglutition and respiration. In light of the results obtained in 18 cases, we report the problems encountered and the surgical technique progressively developed.

The initial assessment of the upper digestive tract and the laryngeal airway is usually performed 1 month after the caustic ingestion, once the critical stage has passed and if reconstructive surgery is considered. It is repeated every month during the stage of active stricture formation and until relative stabilization has occurred. Assessment consists of examination of the buccal cavity looking for retractile scars of the lips, vestibule, floor of the mouth, cheeks, and frenulum as well as assessing the mobility of the tongue, digital palpation of the base of the tongue looking for fibrous infiltration of the muscular bulk, and endoscopy conducted under neuroleptanalgesia or general anesthesia. In the latter case, tracheostomy, if not already performed, may be necessary due to the narrowness of the airway that is often encumbered









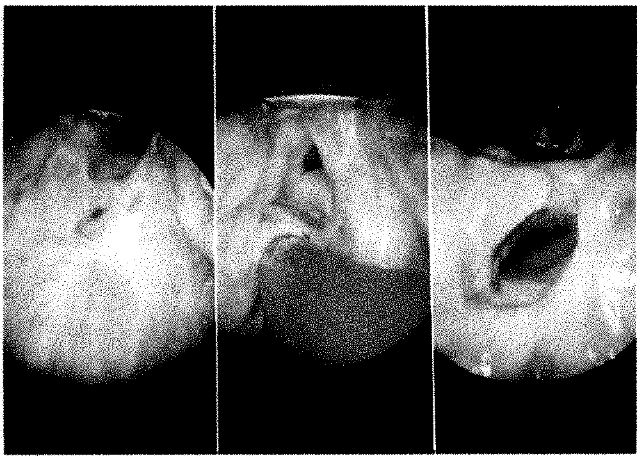


FIG. 1. (*Top left*). Endoscopic classification of the lesions. *Left:* Type I. The left pyriform sinus remains open. Note webs on the posterior wall and adhesion of the arytenoids to the hypopharynx. *Middle:* Type II. Epiglottis is reduced to a suprahyoid stump. The two pyriform sinuses are closed. A narrow laryngeal airway persists. *Right:* Type II. Complete fusion of the epiglottis to the oropharyngeal wall, requiring a tracheostomy. The 2 pyriform sinuses are closed. FIG. 2. (*Top right*). Schematic representation of the surgical procedures used in Type I lesions. FIG. 3. (*Middle left*). Schematic representation of the surgical procedures used in Type II lesions. Note that after resection of the upper part of the thyroid cartilage, the laryngeal inlet is pulled up. FIG. 4. (*Middle right*). Postoperative endoscopic examination. *Left:* at the 14th postoperative day, sutures are still visible. *Middle:* after 1 month. Note the granulation tissue at the anterior part of the anastomosis. *Right:* after 6 months. Note the darker aspect of the ileal mucosa. FIG. 5. (*Bottom left*). Endoscopic management of a stenosis recurring 2 years after reconstructive surgery. *Left:* before dilation. *Middle:* a 28 French bougie is introduced through the stenosis under neuroleptanalgesia. *Right:* result 1 month after 2 sessions of bougienage.

by saliva. In contrast to acute phase management, assessment of chronic injuries is achieved better by a rigid tube than by a flexible fiberoptic examination, because the open hypopharyngoscope provides the endoscopist with the sensitive perception of tissue resistance[13] and facilitates removal of granulation tissues, infiltration of steroids, section of webs, etc.

Although contrast radiography is of no value in assessing the digestive tract, radiologic evaluation may be necessary to evaluate the subglottic or tracheal area. Retrograde fibroscopy *via* tracheostomy is well suited to examination of these regions. The lesions found are generally fairly stereotyped and, from a surgical point of view, may be classified into 2 types (Fig. 1). In type I, the oropharynx may have some stricture but the valleculae are usually preserved. The epiglottis is only partially fused to the lateral wall of the pharynx, and the hypopharynx is incompletely stenosed with one of the two pyriform sinuses remaining open. However, a small bougie introduced into the lumen indicates complete obliteration of the cricopharyngeal sphincter. In type II, the oropharynx contains several fibrous webs and is markedly shrunken with fusion of the base of the tongue to the posterior and lateral walls and disappearance of the valleculae. The epiglottis is unrecognizable, reduced to a suprahyoid stump, and completely or incompletely scarred into the hypopharynx. In this latter case, a passage may persist at the junction of the oropharynx and hypopharynx, behind the epiglottic remnant. Through this small orifice, the laryngeal vestibule may be seen. It is often preserved, but the mobility of the vocal cords is reduced by the fusion of the two arytenoid folds to the posterior wall of the hypopharynx. The two pyriform sinuses are completely closed.

These two types, based mainly on the status of the hypopharynx, must be clearly distinguished, for each implies a different management approach. The surgical decision should take into consideration three essential factors:

1. The evolutivity and the extent of the lesions. Ideally, surgery should not be undertaken before the scarring process is completed. In fact, the contracture tendency of corrosive injuries persists indefinitely, decreasing with time but never achieving complete stability. The operation, therefore, must neither be too early (so as to avoid surgery on any actively inflammatory lesions), nor too late (so as to avoid prolonged hospitalization). In our experience, reconstruction is postponed as long as endoscopic examination indicates mucosal erythema, superficial or deep ulcerations, granulation tissue, or whitish membranes. There must be a minimum of 4 months between the time of caustic ingestion and surgery. Absolute contraindications are represented by massive lesions involving the oropharynx and the buccal cavity. Such extensions may cause trismus, complete immobility of the tongue, and severe retraction of the lips which prevent buccal opening and swallowing.

2. Associated laryngotracheal stenosis. These lesions must be treated before or simultaneously with the digestive stenosis. If performed afterward, it may jeopardize the functional result of reconstructive surgery since the mechanism of deglutition, when successfully restored, always remains precarious.

3. Psychological profile. This factor is of major importance because it governs to a large degree the functional result of the operation. The need for active participation of the patient during the long and difficult postoperative period makes precise psychological evaluation indispensable, analysing especially the reasons for the suicide attempt and the patient's will to recover.

The operation is performed by a double surgical team. It begins with a tracheostomy if the patient does not already have one. The abdominal stage consists of retrosternal isoperistaltic transposition of the ileocolon.[20] It is performed first to ensure that the length of the graft is sufficient to reach the cervical area. In our opinion, this technique presents the following advantages over colon or gastric bypass[21]: (1) safety of its blood supply, allowing a long graft to be obtained; (2) ileal diameter adapted to the oropharyngeal receptor; (3) plasticity and size of the digestive graft allowing it to be placed in the prevertebral space and providing a satisfactory cosmetic appearance of the cervical area; and (4) antireflux effect of Bauhin's valve.

The ileocolic graft is thus mobilized, transposed retrosternally, and introduced into the cervical region behind the medial aspect of the left clavicle. As for the burned esophagus, when emergency removal has not been done, we believe that for previously published reasons[1] esophagectomy can frequently be avoided.

The cervical stage is then carried out. It consists of five essential steps:

1. The skin incision should remain separate as far as possible from that of the tracheostomy. This is to minimize the risk of contamination of the ileal graft and mediastinis from an infection complicating the tracheostomy. We usually adopt an inverted, L-shaped incision.

2. The approach to the pharynx depends on the status of the hypopharynx. In type I lesions (Fig. 2), the pharynx is first entered by suprahyoid transvallecular route. Through this opening, a finger is inserted into the free pyriform sinus. After division of the inferior constrictor, the lateral and inferior aspect of the thyroid cartilage is resected, the mucosa of the pyriform sinus is exposed by the surgeon's finger, and a lateral hypopharyngotomy of about 2 cm is made over the tip of the finger. In type II lesions (Fig. 3), the oropharynx is entered by a transepiglottic approach. As in partial horizontal laryngectomy, the infrahyoid muscles are separated about 1 cm below the inferior aspect of the hyoid bone. The thyroid notch is exposed, and after elevation of the perichondrium, a triangle-shaped piece of the upper half of the cartilage is resected. The laryngeal airway is entered just above the anterior commissure. Epiglottectomy is performed, care being taken not to damage the superior laryngeal pedicles and the mucosa of the vestibular folds.

3. The bed for the ileal graft is then prepared. The carotid artery and the jugular vein are exposed and retracted laterally by division of the thyroid vessels. The

omohyoid muscle is divided. The posterior wall of the pharynx is mobilized from the prevertebral wall by gentle finger dissection.

4. The digestive anastomosis is performed, but its location depends on the type of stenosis. In type I, the ileal graft is sutured to the mucosal edges of the hypopharyngostomy exposed by the finger introduced by the suprahyoid aperture. In type II, an elliptical-shaped, vertical incision is made through the posterior wall of the oropharynx, overhanging the interary tenoid space by about 1 cm. The two edges of the incision are then sutured to the ileum placed in the prevertebral space.

5. The closure of the oropharynx is made following the usual technique of partial laryngectomy. No attempt is made to repair the mucosal defect of the pharynx. The mucosa of the vestibular folds is meticulously sutured to the thyroid perichondrium. About 2 cm of the infrahyoid muscles are resected, and the muscles are resutured so that the larynx is pulled up. No nasal feeding tube is placed across the digestive anastomosis.

The two pharyngeal approaches we adopt depending on the condition of the pyriform sinuses present the following advantages. In type I lesions, the suprahyoid approach combined with a lateral hypopharyngotomy allows, without disturbing the function of the laryngeal vestibule, full evaluation of the lesions, minor surgical procedures such as Z-plasties, excision of focal scars, and/or local grafts under direct vision, good exposure of the remaining pyriform sinus by the finger introduced through the suprahyoid aperture, and precise approximation of the mucosal edges to be sutured. In the literature, lateral hypopharyngotomy has been proposed in case of stricture involving the cricopharyngeal area or part of the hypopharynx.[14-18] In our experience, however, this approach used alone in four patients did not provide such a satisfactory surgical exposure, possibly accounting for the poor results obtained in these cases. In type II lesions, the transepiglottic approach we use differs from that described by Ogura et al.[13] for hypopharyngeal repair in that it is performed at the same time as restoration of digestive continuity and consists of a partial horizontal laryngectomy with resection of the upper part of the thyroid cartilage. Such an approach allows precise assessment of the lesions and anastomosis between the ileum and the pharynx under direct visual control, restoration of the oropharyngeal cavity by mucosal relining of the deep face of the infrahyoid muscles, excision of the supraglottic stricture, thus preventing, or at least limiting, recurrence of the adhesion between the epiglottis and the posterior wall of the pharynx, diminution of aspiration, because the upper traction of the remaining larynx elevates the respiratory tract and thus reduces the declivity of the laryngeal inlet as compared to that of the digestive anastomosis, and combined treatment of eventual laryngotracheal stenosis, when necessary.

The first endoscopic examination is performed between the first and second postoperative week. Granulation tissue is frequently found at the level of sutures and raw areas and must be carefully removed. The patency of the anastomosis is verified and steroids (triamcinolone, 40 mg/ml) are infiltrated in all inflammatory zones (Fig. 4). Thereafter, and when no further surgery is planned, tracheostomy is removed and swallowing instructions are begun with progressive return of the diet to normal within 1 month. Aspirations are frequent but gradually decrease as the ability to swallow develops. The jejunostomy should be maintained at least 1 or 2 months after the return of deglutition to ensure that solid and liquid alimentation is satisfactory and provides stable body weight. Regurgitation was not observed in our series, probably because of the antireflux effect of Bauhin's valve.

The importance of the endoscopic management in the final outcome must be stressed for the stenotic process seems particularly active throughout the postoperative period. Consequently, it is essential to repeat endoscopic examination every week during the first month, every 2 or 3 weeks the next 2 months, and then as needed. Finally, the prolonged stricture tendency of the corrosive injuries accounts for the long-term nature of the disease. As a result, some degree of stricture may recur at the pharyngeal site of the anastomosis and does not represent an abnormal feature. The patient should be clearly advised to visit his physician as soon as dysphagia develops or increases. Although mild stenosis of the anastomosis is easily managed by one or two sessions of peroral bougienage (Fig. 5), complete obliteration may require retrograde dilation by cervical enterotomy.

Conclusion

Hypopharyngeal stricture combined with esophageal obliteration makes restoration of digestive continuity difficult because it impedes normal deglutition and respiration. Careful clinical, psychiatric, and endoscopic evaluation is essential in surgical management. The site of the upper digestive anastomosis depends on the type of lesion encountered. When a pyriform sinus remains open (type I lesion), a suprahyoid approach is used in conjunction with lateral hypopharyngotomy to facilitate the anastomosis and additional minor surgical procedures. When the hypopharynx is completely stenosed (type II lesion), a transepiglottic approach is used, which allows excision of the supraglottic stricture, elevation of the laryngeal tract, suture of the digestive graft to the posterior wall of the oropharynx, and treatment of eventual laryngotracheal stenosis. In both cases, the postoperative and follow-up periods are long and difficult, requiring several endoscopic examinations and often, repeated operations.

In the current study, return of deglutition assuring normal nutrition was obtained in 11 of 18 patients (61%). Experimental studies[6,22] in the future may provide insight into the precise mechanisms of stricture subsequent to ingestion of corrosive materials. Such basic knowledge might allow additional prevention and therapeutic measures to add to the present surgical art and improve the prognosis of caustic ingestion.

Acknowledgments

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Endoesophageal Pull Through

A Technique for the Treatment of Cancers of the Cardia and Lower Esophagus

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Transthoracic and extrathoracic approaches to cancers of the lower esophagus and cardia each have advantages and drawbacks; the trauma of thoracotomy must be balanced against that of blunt mediastinal extraction of the esophagus. A different surgical approach is proposed in this paper, avoiding both thoracotomy and encroachment upon thoracic mediastinal structures. This technique is based on the removal of the tumor and the esophageal mucosa above it as a distinct anatomic layer by blunt dissection through separate abdominal and neck incisions. This is followed by pulling upward a segment of stomach (or colon) through the esophageal muscular tunnel into the neck for a cervical anastomosis. This endoesophageal pull through (EEPT) approach has been used in the surgical treatment of a total of ten patients, six with adenocarcinomas of the cardia and four with squamous cell carcinomas of the lower esophagus. In nine patients the stomach, and in one patient the left colon, was brought to the neck to reestablish gastrointestinal (GI) continuity. The operation was well tolerated. There was no excessive intraoperative or postoperative bleeding, and there was no in-hospital mortality up to 30 days. The major postoperative complication was cervical anastomotic leakage seen in four patients. The EEPT technique is a palliative approach for cancers of the lower esophagus and cardia, comparing favorably with the standard extrathoracic or transthoracic transhiatal procedures.

THE SURGICAL TREATMENT of cancers of the lower esophagus and cardia consists of resection of the tumor-bearing area followed by reestablishment of gastrointestinal (GI) continuity. The conventional transpleural approach with an intrathoracic esophagogastrostomy has been challenged by the extrathoracic approach with anastomosis performed in the neck.[1-3] Avoidance of thoracotomy is undoubtedly of value in debilitated patients with poor lung function. The hazards of a cervical anastomosis carry a small morbidity rate. There are reservations about a blunt, essentially blind extraction of the intrathoracic esophagus, a procedure believed by some to be inherently less safe than resection under direct vision.[4,5]

A contrasting surgical approach to cancers of the lower esophagus and cardia, an endothoracic endoesophageal pull through (EEPT) technique is now proposed. The tumor and the esophageal mucosa above it are removed by digital dissection, and the esophageal muscular tunnel that remains, its blood supply intact, used as a conduit to bring a segment of the GI tract to the neck for cervical anastomosis. Stripping of the mucosal sleeve is done entirely from within the abdomen and through the neck. A thoracotomy is not necessary, and no extraesophageal mediastinal dissection is done.

Materials and Methods

The initial attempt at esophageal mucosal stripping was carried out on a fresh autopsy specimen. It was found that the normal esophageal mucosa could be readily freed of its submucosal bed and extracted intact almost effortlessly from within its encasing muscular layer.

To test the surgical feasibility of the technique, three successive patients with cancers of the cardia and middle and lower esophagus were first operated on by a conventional transthoracic approach putting to test the concept of esophageal mucosa stripping. Two patients, a 55-year-old male and a 65-year-old female, had cancers of the lower esophagus and cardia, respectively. The third patient, a 65-year-old female who had a distal gastrectomy performed for antral carcinoma 4 years earlier presented a squamous cell cancer of the middle third of the esophagus.

A left posterolateral, thoracoabdominal incision was performed in these three preliminary cases, entering the chest through the sixth interspace. The tumor was re-

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TABLE 1. *Clinicopathologic Summary of Patients Treated by the EEPT Technique*

Patient	Age	Sex	Pathology	Organ Used for Reconstruction	Complications; Follow-up Results
A	61	M	Adenocarcinoma of cardia; many involved nodes.	Stomach	Anastomotic leakage, later ceased; died suddenly at home 2.5 months after operation.
B	55	F	Adenocarcinoma of cardia; no grossly involved nodes.	Stomach	No complications; no recurrence at 6 months.
C	54	F	Adenocarcinoma of cardia; no grossly involved nodes.	Stomach	200 mL right pleural effusion; no recurrence at 5.5 months.
D	65	F	Squamous cell carcinoma of lower esophagus.	Stomach	Anastomotic leakage with late stricture; no recurrence at 5 months.
E	52	M	Unresectable adenocarcinoma of cardia; liver metastases.	Stomach	Postoperative atelectasis, left upper lobe; eating, but losing weight.
F	50	F	Squamous cell carcinoma of lower esophagus.	Stomach	Intermittent anastomotic leakage for 3 weeks; no recurrence at 4 months.
G	49	M	Infiltrating carcinoma of stomach, total gastrectomy done.	Left colon	Slightly hoarse, eating well; no recurrence at 4 months.
H	52	M	Squamous cell carcinoma of lower esophagus.	Stomach	No complications; no recurrence at 3.5 months.
I	60	M	Squamous cell carcinoma of lower and middle esophagus.	Stomach	350 mL right pleural effusion; transient cardiac arrest; no recurrence at 3.5 months.
J	55	F	Adenocarcinoma of cardia; preoperative esophageal perforation.	Stomach	Anastomotic leakage; preoperative empyema controlled at 3 weeks.

sectable in all three cases. For the first two patients the distal stomach was mobilized and brought into the left chest, keeping intact the right gastric and right gastroepiploic vessels. For the third patient, because of a previous distal gastrectomy, an isoperistaltic segment of left colon was mobilized using the ascending branch of the left colic artery as the nutrient vessel.

In all of these cases the normal esophageal wall was opened a few centimeters below the level of the aortic arch in a plane between the muscular and mucosal layers. The inner mucosal sleeve was freed along its entire length by digital dissection, working at first from within the chest and next through a separate incision in the neck. It was delivered intact without any excessive bleeding. GI continuity was reestablished by pulling the prepared stomach in two patients and the colon segment in the third under direct vision through the remaining esophageal muscular tunnel into the neck for a cervical anastomosis.

All three patients had a satisfactory postoperative course and were taking liquids and semisolids at the time of discharge 7–10 days postoperatively.

Ten consecutive patients with cancers of the lower esophagus and cardia were then operated upon in a uniform manner, using the EEPT technique without thoracotomy.

Clinical Material

There were five men and five women in this series, whose ages ranged from 49 to 65 years (Table 1). The presenting complaint in nine cases was progressive dysphagia and weight loss. Only one patient had chronic upper abdominal pain. Six patients had adenocarcinoma of the cardia and four had squamous cell carcinoma of the lower esophagus. All patients had a preliminary barium swallow. The diagnosis was established in all cases by endoscopic biopsy, except in the last case where the lower esophagus was perforated during esophagoscopy elsewhere, and the diagnosis made subsequently at laparotomy. Five patients were chronic smokers, but none had any clinically significant pulmonary or cardiac disorders. One patient gave a history of melena requiring blood transfusion a few weeks before admission. This patient had a hemoglobin level of 10 mg/dL; that of the others ranged from 11.5 to 15 mg/dL. No preoperative hyperalimentation was carried out. One patient was found at operation to have a linitis plastica type of gastric tumor involving the whole stomach. In one patient the tumor proved, despite all attempts, to be unresectable; the EEPT procedure was done in both these cases despite these features, wholly as palliation.

Operative Technique

With the patient in the supine position and the head turned to the right, the entire abdomen, anterior chest, and left neck areas are exposed, cleansed and appropriately draped. The left arm in full extension is kept abducted to the side and only the right arm is used for

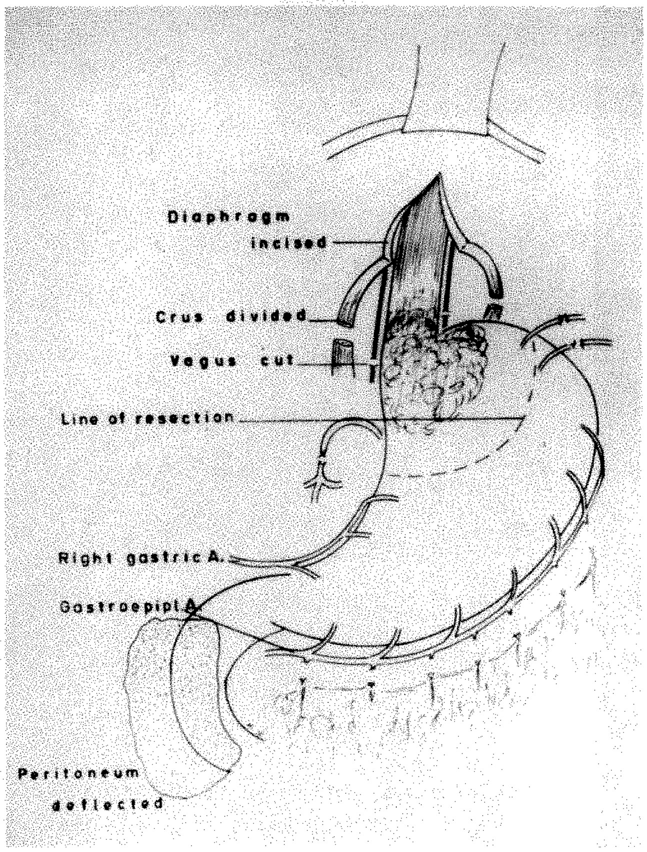


FIG. 1. The entire stomach is first mobilized. Proximally, both crural limbs are divided and that part of the diaphragm arching over the esophagus is incised upwards for about 5 cm to provide maximal exposure of the lower esophagus well above the tumor mass. The vagus nerves are cut. Distally, a generous Kocher maneuver is performed, allowing free upward traction of the stomach and duodenum. The left gastric and short gastric arteries are divided and ligated. The right gastric and gastroepiploic arteries are preserved as nutrient vessels. The line of gastric transection lies about 5–6 cm below the palpable lower margin of the tumor mass.

insertion of arterial and venous lines. A large sized nasogastric tube is passed and kept in place.

The abdomen is first opened through a long midline upper abdominal incision extended to below the umbilicus. After excision of the xyphoid, a fixed sternal retractor is applied to the upper part of the abdominal incision to provide maximum exposure of the lower mediastinum. General abdominal exploration is carried out to determine the extent of the tumor's growth and its resectability, and to establish the presence or absence of metastatic disease.

The esophagogastric junction is exposed after the left lobe of the liver is detached at its triangular ligament from the diaphragm and deflected to the right (Fig. 1). The tendinous portion of the diaphragm arching over the esophagus is incised upwards in the midline until the pericardium is exposed. This opens up the lower mediastinum as viewed from the abdominal side. Even greater access is achieved by transecting the two limbs of the diaphragmatic crus. The two vagus nerves are also cut, allowing further downward traction and better exposure of the esophagus above the tumor itself.

The stomach, along with the tumor mass, is mobilized and separated from the posterior abdominal wall and surrounding structures, taking as many nearby grossly involved nodes as is practicable. The left gastric artery is divided at its origin. The right gastric and gastroepiploic vessels are carefully preserved, and their omental branches individually ligated. The spleen is not removed, but the short gastric vessels are divided. A generous Kocher maneuver is carried out all the way to the lower end of the duodenal loop, such peritoneal deflection allowing the whole distal stomach and duodenum to be pulled cephalad without tension. The stomach is transected along a line some 5–6 cm from the lower palpable border of the tumor mass. The pyloric ring is successively dilated with Hegar dilators to a maximum size of #17, in preference to a pyloromyotomy or pyloroplasty. The upper end of the stomach is closed in two layers, an inner with catgut and an outer with silk sutures.

Attention is now turned to the specimen side (Fig. 2). With a tape around the gastroesophageal junction the tumor is pulled downwards. Two medium sized retractors are placed into the lower mediastinum on either side of the esophagus pushing the two pleura away but avoiding any pressure on the heart. With the lower esophagus fully exposed, its muscular layer is incised circumferentially about 3–5 cm above the palpable margin of the tumor. This is carried down to the readily identifiable mucosal layer. The two cut ends of the muscular layer spring apart as the specimen is retracted downwards. The tip of the index finger pointing upwards is now inserted in the plane between the outer muscular and the inner mucosal layer. With the upper rim of the muscular layer held apart by heavy traction sutures or Babcock clamps, the exploring index finger is insinuated into the loose submucosal layer of the thoracic esophagus. The indwelling nasogastric tube serves to identify the mucosal sleeve as finger dissection is continued upwards. Digital detachment of the mucosa from the muscle is continued upwards as far as possible, and in any case beyond the level of the aortic arch and carina, both of which are palpable. There is no risk of breaking through the muscular esophageal wall into the mediastinum as long as the tip of the index finger follows the course of the nasogastric tube. Mucosal stripping is greatly facilitated by continuous downward traction on the specimen. There is little active bleeding and no vessels are encountered that would require ligation or cauterization.

The cervical esophagus is next exposed through a long incision parallel to the anterior margin of the left sternocleidomastoid muscle (Fig. 3). It is mobilized and lifted into view by an encircling rubber tape, taking care not to put any pressure on the general course of the recurrent laryngeal nerve. The distal esophagus is not dissected out any further than the thoracic inlet. The pulled up esophagus is incised circumferentially down to its mucosal layer. Separation of the mucosal sleeve is now begun as from the abdominal side. Holding apart the edges of the distal muscular layer with heavy traction sutures or Babcock clamps, the tip of the index finger is inserted into the readily found plane between the mucosal and muscular layers. It is pushed downwards in a spiraling fashion around the mucosal sleeve, feeling all the time the indwelling nasogastric tube. The operator, standing on the patient's left side, can insert the right index finger downwards from the neck and the left index finger upwards from the abdomen until they meet in the newly established plane. Bimanual dissection is continued until the whole mucosal sleeve is felt to be separated from its encasing muscular envelope. At this stage the mucosal sleeve is transected in the neck and its whole length extracted intact from the abdomen. It may not come out as readily as expected. By grasping the specimen and exerting gentle and unremitting traction downwards, the entire thoracic esophageal mucosal sleeve is pulled out in one piece while still attached to the specimen below (Figs. 4A and B). There is remarkably little bleeding from inside the denuded muscular tunnel, and what bleeding occurs stops spontaneously within a few seconds. Using the indwelling nasogastric tube as a guide, the index fingers of the two hands can be reinserted from above and below to further dilate the muscular channel by gentle lateral pressure.

The mucosal coring out process can be easy or difficult depending on the completeness of the blunt digital dissection. An eversion maneuver can also be used by removing the initial nasogastric tube and inserting another one through a small hole made into the mucosal sleeve just above the tumor. This tube is pushed into the neck and its tip tied to the mucosal sleeve and pulled out from below. Neither forceful extraction nor vigorous pulling is needed if digital dissection has been thorough.

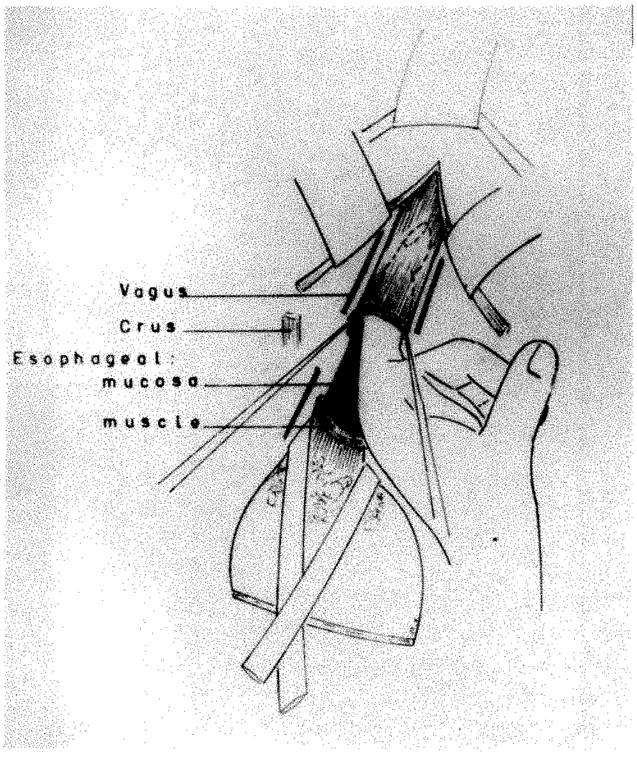


FIG. 2. The fundus of the stomach, involved by cancer of the cardia or attached to a lower esophageal cancer, has been separated from the rest of the normal stomach. The esophageal muscular layer has been incised circumferentially down to its mucosal layer. Downward traction on a tape placed around the gastroesophagel junction exposes a segment of the intact mucosal tube. Holding apart the upper rim of the muscular layer, the index finger is pushed into the plane between the esophageal muscle and mucosa to begin digital separation of these two layers upwards into the thorax.

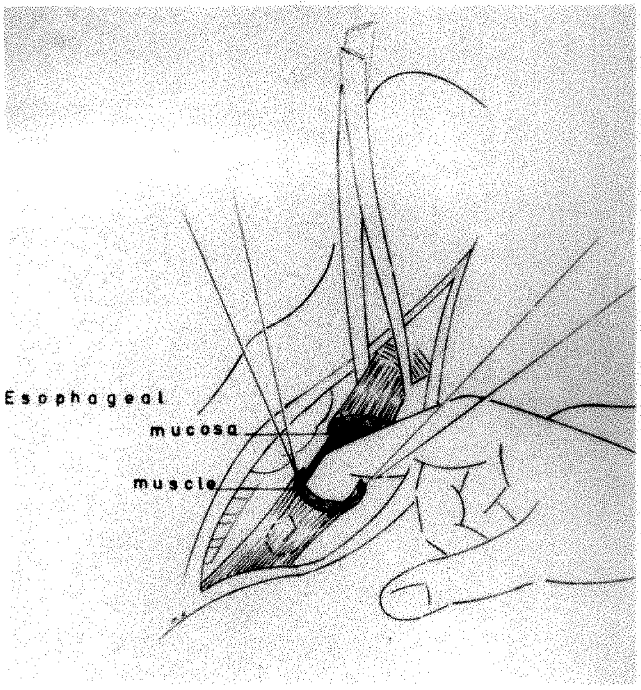
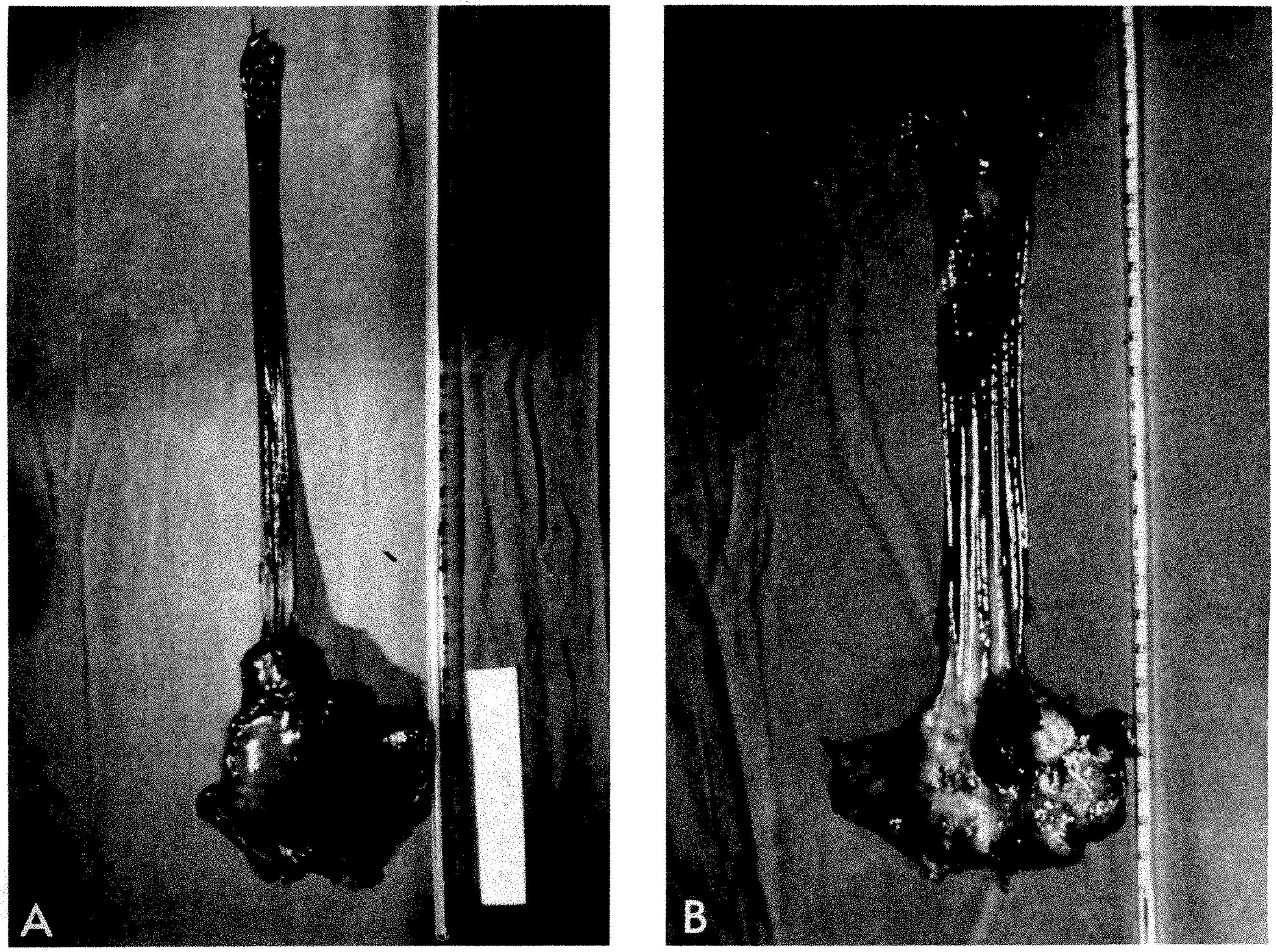


FIG. 3. The cervical esophagus has been exposed through an incision parallel to the anterior border of the left sternocleidomastoid muscle, and has been lifted out from behind the trachea. Its muscular layer has been incised circumferentially down to the mucosal layer. Pulling upwards on a tape placed around the upper part of the cervical esophagus creates a gap between the two ends of the divided muscular layer. Holding apart the rim of the distal muscular wall with traction sutures, the tip of the index finger is insinuated between muscle and mucosa, and digital separation of these two layers is continued downwards into the thorax.



FIGS. 4A and B. *A*. The removed but unopened specimen of Patient C showing the gastric fundus involved by an adenocarcinoma of the cardia. A short segment of esophageal muscle projects upwards from the fundus. The full length of the stripped-off esophageal mucosal sleeve remains attached to the specimen. *B*. Same specimen, opened.

The previously prepared gastric or colon segment is next pulled into the neck from within the esophageal muscular channel for a cervical anastomosis (Fig. 5). The apex of the stomach, or closed proximal end of the colon, is fixed temporarily to the blunt end of an indwelling catheter. Pulling on the tip of the catheter from the neck with the right hand, the surgeon's left hand guides the bowel segment up into the lower opening of the muscular tube and out its upper end in the neck, avoiding any stretching or axial rotation. An end-to-side one layer esophagogastrostomy, or esophagocolostomy, is carried out in the neck between the proximal esophagus and a convenient site on the gastric or colonic wall. A small bore plastic catheter is put down through the nose by the anesthetist, and threaded across the anastomosis for temporary postoperative decompression of the pulled-up bowel segment. A narrow penrose drain is inserted down to the thoracic inlet region and the cervical incision closed.

A temporary feeding jejunostomy is performed, bringing the end of the jejunostomy catheter out in the left lower quadrant. The abdomen is closed without drainage. A chest film is taken in the operating room to detect and treat any unsuspected pneumothorax.

Clear fluids in small portions are started by mouth on about the third or fourth day if the abdomen is soft and peristalsis is present. Oral feedings are gradually increased in amount, and soft solids added by about the seventh postoperative day. Jejunostomy feedings are begun if there is any doubt about the patient's ability to tolerate sufficient fluids by mouth, or if there are signs of cervical anastomotic leakage.

Results

There was no 30-day postoperative mortality rate. Patient A died suddenly at home 2½ months after operation, presumably from a myocardial infarction. The other nine patients have been seen postoperatively at regular monthly intervals, the longest follow-up period being 6 months, the shortest 6 weeks. Postoperative complications, were of two types. The first consisted of pulmonary problems, mainly atelectasis and pleural effusion. The latter varied from 200 to 350 mL in amount and was seen mostly on the third to fifth postoperative day. During thoracentesis Patient I experienced transient cardiac arrest, which reverted promptly and without untoward results. There were no wound infections, and no patient had to be reexplored for bleeding or deep-seated localized sepsis. Patient G remains somewhat hoarse, most likely because of damage to the left recurrent nerve during mobilization of the cervical esophagus.

The other type of complication was leakage from the cervical anastomosis. This occurred in four patients. Leakage stopped within about 4 days in one case, but the patient had to be readmitted a month later for surgical release of an anastomotic stricture after two dilatations had failed to enlarge the narrowed area. Leakage stopped spontaneously within about 3 and 7 days, respectively, in the second and third cases. In a last patient the leakage continued intermittently for some 3 weeks after discharge from hospital without interfering with normal eating.

In terms of palliation, namely, the ability to eat comfortably and gain weight, all ten patients were satisfied with the results following operation.

Discussion

The concept behind the EEPT technique is not a new one. Essentially, one segment of bowel is pulled through the lumen of another segment from which the mucosal lining has been removed, thereby avoiding damage to the latter's outside structures. For the lower end of the GI tract this technique has proven suitable in the treatment of Hirschsprung's disease and familial polyposis of the colon since pelvic structures outside the rectum are not injured. For the upper end of the GI tract certain esophageal disorders should, theorectially, also be amenable to such an approach. Whatever segment of the GI tract is passed from the abdomen into the neck, it is kept within the anatomic confines of an esophageal muscular tube, avoiding injury to mediastinal structures. This pathway is also the shortest of all available routes to bridge the gap between the two ends of the alimentary tract after an esophagectomy.

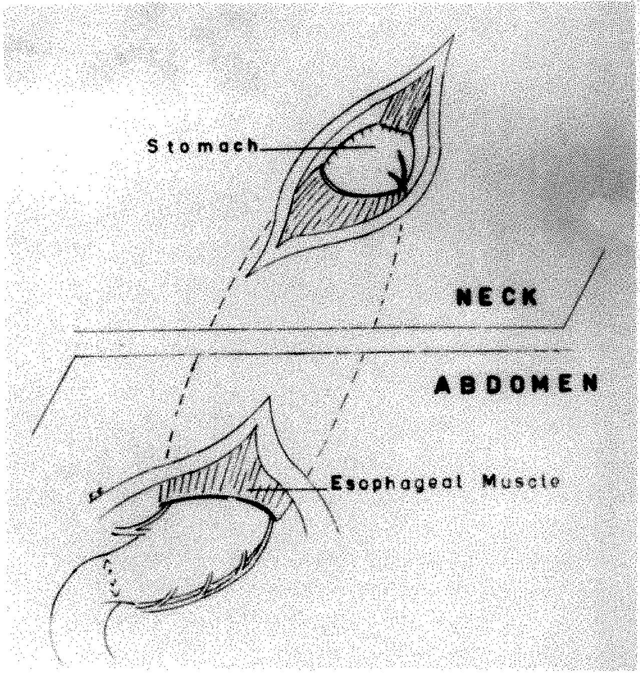


FIG. 5. The previously prepared distal stomach has been pulled from the abdomen into the neck through an accommodating thoracic esophageal muscular tunnel, and the cervical esophagogastrostomy has been completed.

Surgeons have known for some time that the mucosal lining of the esophagus is its strongest layer. This nonkeratinized squamous epithelium can be separated from the loose areolar type of connective tissue of the underlying submucosa with surprising ease, with some of the submucosa remaining attached to the mucosa. The intramural intrinsic blood supply of the esophagus was studied by Potter and Holyoke in 1950.[6] Segmental arterial branches of the aorta were found to penetrate at right angles the outer longitudinal and inner circular muscle bundles to become rapidly lost in the highly distensible submucosal layer. This could explain the paucity of active bleeding after stripping of the esophageal mucosa. In the endorectal pull through technique infiltration with saline or epinephrine solutions is sometimes necessary to facilitate dissection and minimize bleeding. Such measures need not be taken during removal of the esophageal mucosa.

Apparently Rehn in 1914 first proposed extraction of the esophageal mucous membrane to avoid bleeding.[7] The proposition was not applied clinically. One reason for this may have been the fact that resection of the esophageal tumor itself, in the hope of a possible cure, has always been foremost in the minds of surgeons. Revival of esophagectomy without thoracotomy, and its recent popularity in some center,[8–10] may also have kept dormant the idea of esophageal mucosal stripping.

TABLE 2. *Published Reports on Postoperative Leakage from Cervical Esophagogastrostomy*

	Technique of Cervical Anastomosis	No. of Patients Operated	No. of Patients with Leakage (%)
Barbier et al.[13]	Two layer	25	9 (36)
Caracci et al.[5]	Two layer	9	2 (22.2)
Finley et al.[1]	Not stated	34	7 (20)
Goldfaden et al.[8]	Two layer	29	2 (7)
Orringer[14]	Two layer	92	3 (3)
Shahian et al.[15]	Not stated	26	4 (15.4)
Steiger and Wilson[16]	Two layer inkwell	21	4 (19)
Tryzelaar et al.[17]	Two layer	13	1 (8)

That esophageal stripping and the passing of a segment of bowel through the remaining muscular tunnel is technically possible, and can be done with relative ease and negligible blood loss, was shown in our preliminary three cases using the direct vision transpleural route. It was reasoned that by restricting the technique to tumors of the lower esophagus and cardia, a thoracotomy would not be necessary at all, while extraesophageal mediastinal structures could be kept out of surgical harm's way. This assumption was substantiated on the basis of the clinical experience with ten consecutive cases of cancers of the lower esophagus and cardia. For malignancies in this location the vagus nerves had to be cut since they ran too close to the tumor. However, should the EEPT technique prove applicable to treatment of some benign lesions of the esophagus, the vagus nerves could well be spared.

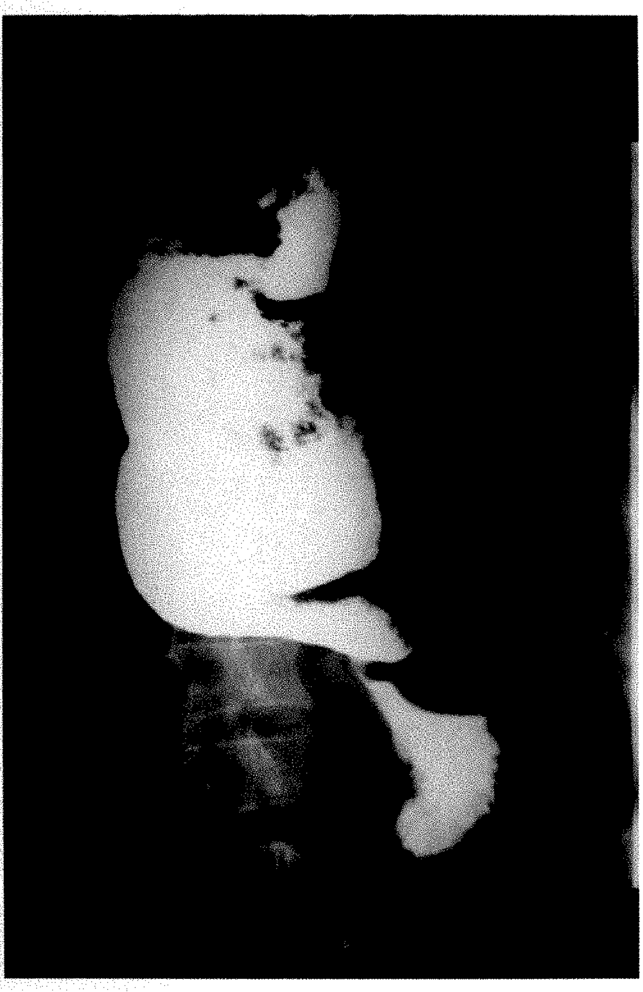


FIG. 6. Barium swallow of patient H showing free expansion of a functional stomach resting within the esophageal muscular tunnel.

There was no 30-day in-hospital mortality rate in this group of ten patients. This was perhaps related to the relatively young age of patients in this series as compared to esophageal cancer patients in general. None of the ten patients in whom EEPT was performed was either severely debilitated or suffered from any serious pulmonary disorders. None had severe anemia or needed preoperative nutritional preparation, and none required postoperative pulmonary support. The average operative blood loss was less than 800 mL; only Patient E with an unresectable tumor received about 1500 mL of whole blood during unsuccessful attempts at its removal. Avoidance of thoracotomy was not the overriding reason for using the EEPT technique in any of these ten patients. Nevertheless, the clear impression was that their overall postoperative course was relatively benign. And this might well be attributed to avoidance of thoracotomy.

The pleural space was not knowingly entered during the operation, and such postoperative pulmonary problems as consolidation and effusion were managed with relative ease. No mediastinal bleeding, tracheal injury, or chylothorax, as has been reported for transhiatal esophagectomy,[11,12] was encountered.

Leakage from the cervical anastomosis in four patients was more disconcerting. It stopped spontaneously or became insignificant within a matter of days. This incidence of anastomotic leakage was greater than that reported for other series of patients treated by the extrathoracic approach (Table 2). It seems unlikely that pressure from the encasing esophageal muscular tunnel could have caused relative ischemia at the apex of the pulled-through stomach in the neck. The esophageal muscular tube was found to be thin-walled, distensible, and not compressing its new contents. Barium swallow of Patient H taken 2 weeks postoperatively, showed a commodious stomach (Fig. 6). In none of the four patients who developed cervical leakage was there any particular difficulty encountered in bringing the stomach up into the neck. Intraluminal dilatation of the pyloric sphincter with Hegar dilators, instead of pyloroplasty or pyloromyotomy, was also an unlikely reason since it was done for all patients. The real culprit may well have been the use of a single layer suture for the cervical anastomosis in this series. A two-layer technique is planned for future cases.

Stripping of the esophageal mucosa was not easy at times in the beginning. But once digital detachment of the mucosa from the muscular layer was complete, the entire mucosal sleeve could be extracted atraumatically in every case with gentle and steady traction. Likewise, guiding the stomach or colon into the neck required patience as well as judgment regarding the required length of the prepared bowel segment, while paying attention to avoid axial rotation.

The procedure was deliberately restricted to cancers of the cardia and lower esophagus. Certain limitations as well as possible expansion of the scope of the operation were noted.

The exact location of tumor in Patient I was misjudged on barium swallow and found at operation to reach higher than expected. This confirmed a prior suspicion that even with maximal exposure of the lower esophagus through the abdomen, mucosal stripping would not be easy if the tumor extended very high above the gastroesophagal junction. Digital dissection of the mucosal sleeve would appear to be difficult to start under direct vision if the upper border of the esophageal cancer lies higher than 12–15 cm above the gastroesophageal junction. For this reason EEPT without thoracotomy would not seem applicable to middle and upper third esophageal cancers. No cases with primary cervical esophageal cancer were seen during the study period, but tumors at this level would seem eminently suitable for treatment with the EEPT technique.

On the other hand, distal extension of the tumor presented no technical problems but provided a new opportunity. Patient G was found to have a linitis plastica type of cancer involving the whole stomach. There were no obvious liver metastases, and total gastectomy was readily carried out. GI continuity was reestablished in this case by guiding an isoperistaltic segment of left colon through the esophageal muscular tunnel into the neck for a primary cervical anastomosis. The final colonic food resceptacle was more spacious than any that could have been fashioned by the use of a jejunal loop (Fig. 7). The additional cervical anastomosis in this case was worth the larger gastric pouch created. This patient was eating a full-course meal three times a day, and had gained 5 kg in weight on follow-up visit 4 months later. In Patient E the EEPT technique became essentially a bypass maneuver for an unresectable cancer of the cardia. The mobilized distal stomach in this case was pulled up alongside the unresectable tumor and guided through the esophageal muscular tunnel for a cervical anastomosis. The patient was alive and eating comfortably when seen about 4 months after discharge from the hospital but had continued to lose weight.

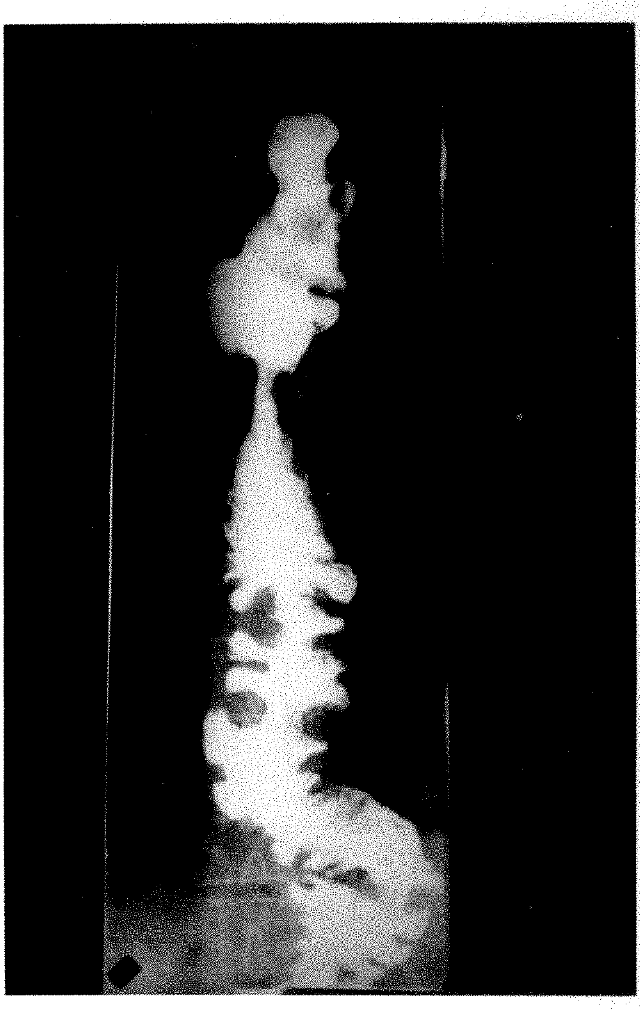


FIG. 7. Contrast study in Patient G after isoperistaltic left colon interposition within an accommodating thoracic esophageal muscular tunnel.

Cancers of the esophagus and cardia are said to advance submucosally upwards for a distance of about 5–6 cm.[18] To clarify this point, the lower 5-cm portion of the esophageal mucosal sleeve attached to and extending above the resected specimen was sectioned at 1-cm intervals and studied histologically. No proximal submucosal extension of the tumor could be seen beyond the 1-cm level from the upper margin of the tumor. The rim of the esophageal muscle projecting upwards from the proximal part of the specimen was also examined histologically and found not to be involved by tumor in any of the removed specimens.

The proposed EEPT approach is in accord with the view that all symptomatic patients with cancer of the esophagus should be operated on—for palliation if possible, and for cure if circumstances are fortunate.[19] In terms of relieving their distressing dysphagia and allowing them to eat comfortably and return to normal life within a short time, this operative approach was well received by all ten patients in this series.

The EEPT technique is basically a palliative operation for cancers of the lower esophagus and cardia. As such, it should be compared with the other two palliative approaches available for tumors of this location, namely, the conventional transthoracic and the transhiatal extrathoracotomy operations. The *en bloc* removal of all expendable surrounding normal structures is curative by design.[20] The limits of tumor resectability and the opportunity for lymph node removal with the EEPT technique are the same as with the other two palliative approaches. The distance of the gastric transection line from the lower margin of the tumor is also the same. The upper level of mucosal resection margin is as high as it could conceivably be. An occasional cure will be achieved with either of the two standard palliative approaches if the cancer happens to be at an early stage of its growth. The total number of cases in this series has been too small and the follow-up time too brief to permit any statement regarding the likelihood of cure in any of the ten patients in whom resection of the whole tumor with removal of all involved contiguous nodes was carried out.

Editor's Note

The author has provided the following additional information.

Since submission of the manuscript, seven additional cases with squamous cell cancer of the lower esophagus or adenocarcinoma of the cardia were operated on in a uniform manner using the endoesophageal pull through technique described. Two male patients aged 79 and 83 died in the immediate postoperative phase, the first of massive myocardial infarction and the second with superior mesenteric artery occlusion and bowel gangrene. Of the remaining five patients two developed transient leakage from the cervical esophagogastrostomy. The additional experience with these seven patients reconfirmed the need to develop with meticulous care the anatomic plane between the esophageal mucosa and muscle, both in the abdomen and in the neck.

Follow-up on all patients reported initially shows that of the three preliminary cases operated on by the standard transthoracic approach, one is alive at 10 months and two died, having died at 10 and 9 months, respectively. Of the ten cases in whom a thoracotomy was not done and the stomach or colon was guided through the denuded esophageal muscular tunnel for a primary anastomosis in the neck by this EEPT method, three have died at 2.5, 5, and 6 months, respectively. The remaining seven patients operated on by the EEPT technique are alive and eating comfortably, the longest survival being 11 months, the shortest 5 months. Among the survivors is the patient who underwent total gastrectomy with left colon pull through into the neck without opening the chest.

Acknowledgments

The expert anesthesiology management of Dr. Mohammad Rezvan is gratefully acknowledged. I want to thank Dr. Hakob Papazian from the Department of Pathology of Modarress Hospital for pathological studies performed, and Dr. Francis D. Moore of Harvard Medical School for reviewing and editing the manuscript.

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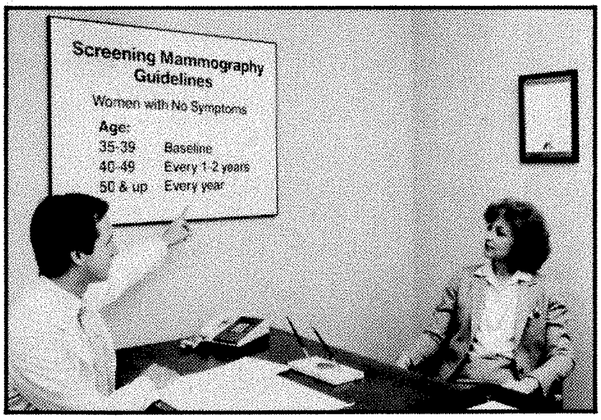

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Prognostic Significance of DNA Aneuploidy in Stage I Cutaneous Melanoma

SONIA M. KHEIR, M.D.,* STEVEN D. BINES, M.D.,* JAMIE H. VONROENN, M.D.,† SENG-JAW SOONG, PH.D.,‡ MARSHALL M. URIST, M.D.,§ and JOHN S. COON, M.D., PH.D.*

The prognostic significance of DNA aneuploidy was studied retrospectively in 177 Stage I cutaneous melanomas. DNA content was determined by flow cytometry of propidium iodide-stained nuclei recovered from formalin-fixed, paraffin-embedded material. Of 162 evaluable histograms, 124 were diploid, 35 aneuploid, and 3 tetraploid. Aneuploidy strongly correlated with established predictors of unfavorable prognosis, namely, thickness $p < .005$, level $p < 0.005$, ulceration $p < 0.005$, and presence of vertical growth phase $p < 0.02$. Overall, aneuploidy was strongly correlated with recurrence ($p < 0.005$) and shorter disease-free survival ($p < 0.0001$). Aneuploidy was an independent predictor of recurrence for tumors < 1.5 mm thick ($p < 0.0001$) and ≥3 mm thick ($p = 0.031$). For melanomas 1.5–2.9 mm thick, aneuploid tumors had a 27% higher recurrence rate than diploid tumors (63% *vs.* 36%). This was not statistically significant ($p = 0.247$). In a multivariate analysis of common predictors stratified by thickness, DNA aneuploidy was the most significant independent parameter ($p < 0.002$). DNA content appears to be an important stratification parameter for Stage I cutaneous melanoma.

From the Departments of Pathology and General Surgery, Rush Presbyterian St. Luke's Medical Center, Chicago, Illinois; the Department of Medicine, Section of Medical Oncology, Northwestern University, Chicago, Illinois†; the Biostatistics Unit, School of Medicine/Comprehensive Cancer Center, University of Alabama, Birmingham, Alabama‡; and the Division of Surgical Oncology, University of Alabama, Birmingham, Alabama§*

PATIENTS presenting with Stage I cutaneous melanoma have a highly variable clinical course. This variability has resulted in the description of numerous histologic and clinical prognostic factors used to help in the development of treatment plans. The most important of these factors includes level of invasion, tumor thickness, ulceration, vertical growth phase, cell type, mitotic index, host inflammatory cell response, regression, location of lesion, and patient sex.[1-10] While none of these is ideal, tumor thickness appears to be the most highly predictive factor, whether considered alone or in combination with other parameters.[11]

Using tumor thickness, patients can be identified who have either an excellent prognosis (lesions < 0.76 mm thick) or poor prognosis (lesions > 4 mm thick). However, exceptions to this rule exist no matter how thickness is used to stratify melanoma patients. Additional prognostic methods are clearly needed since it is evident that morphologic parameters are not always adequate to predict the biologic behavior of melanomas.[12]

The value of DNA content determination by flow cytometry (FCM) in predicting biologic behavior has been strongly suggested in several solid tumor models.[13-15] Recently, it has been shown that formalin-fixed, paraffin-embedded primary melanomas can be conveniently and reliably prepared for analysis by FCM.[16-18] Furthermore, this same report suggested that the presence of abnormal DNA content (DNA aneuploidy) in primary cutaneous melanomas correlates with increasing tumor thickness and incidence of recurrence. The conclusions that could be drawn from this study were limited by the small patient base, lack of survival data, and lack of a multivariate analysis of DNA aneuploidy in relation to other accepted prognostic factors. We sought to address these shortcomings in the present study of 177 patients with primary Stage I cutaneous melanoma. This new study shows that DNA aneuploidy is highly predictive of recurrence and shorter disease-free survival when this factor is considered alone. More importantly, it is also highly significant in a

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multivariate analysis in which the other significant prognostic factors are considered.

Materials and Methods

Patient Selection

The study material consisted of single paraffin blocks from each of 177 primary cutaneous melanomas from 177 patients. This material originated from three sources: Rush Presbyterian St. Luke's Medical Center, Chicago, IL (63 patients); Baptist Hospital, Birmingham, AL (22 patients); and the University of Alabama Melanoma Registry, Birmingham, AL (92 patients). Cases were selected on the basis of paraffin block availability and included all Stage I melanoma patients seen between 1969 and 1985 at Rush. Only those lesions initially fixed in buffered formalin prior to paraffin embedding were included for study (material fixed in most other common fixitives, for example, Bouin's, has been shown to be unsuitable for this technique).[19]

A hematoxylin and eosin-stained section of each case was studied without previous knowledge of the FCM data. Each case was evaluated according to Breslow's thickness, Clark's level, growth pattern (radial *vs.* vertical), cell type, presence of ulceration, and mitotic index.[5,20-24] Initial clinical data collected for each patient included patient age, patient sex, and anatomic location of the lesion.

Follow-up data were obtained from tumor registry records, hospital and office charts, and by direct patient contact. Patients dead of unknown cause without documentation of recurrence prior to death (two patients) were excluded from the study. Similarly, outpatients without documented follow-up were excluded from the study (12 patients).

Sample Preparation

All blocks processed for FCM were chosen to be representative of the tumor after evaluation. Preparation of the blocks was accomplished with a modification of the method of Hedley et al.[17,25] Thick sections (50 μm) from formalin-fixed, paraffin tissue blocks were dewaxed in xylene, rehydrated in graded ethanol solutions, and mechanically minced with scissors. The tissue slurry was then digested with 0.5% pepsin (Sigma, St. Louis, MO), in 0.9% NaCl at pH 1.5 for 30 minutes at 37 C to produce a suspension. The suspensions were further treated with Nonidet P40 (Sigma) and trypsin type IX (Sigma) according to the method of Vindelov et al.[26] to aid the production of a monodisperse suspension of bare nuclei. The suspension was washed, filtered through 41-μm nylon mesh to remove aggregates, and the concentration was adjusted to 2×10^6 nuclei/mL. The nuclei were then incubated for 10 minutes with 0.1 mg/mL Ribonuclease-A (Sigma), then stained for DNA with propidium iodide (Sigma) at 0.13 mg/mL for 15 minutes, and analyzed by FCM within 1 hour of staining. A conventional histologic section adjacent to the thick section was prepared in each specimen to verify the presence of tumor in the material prepared for FCM.

FCM Analysis

Nuclei were adjusted to a concentration of 5×10^5 nuclei/mL in dimethylsulfoxide-citrate buffer for FCM analysis as described previously.[27] The relative DNA content (red fluorescence) of 10^5 nuclei was analyzed in a Coulter Epics V (R) (Hialeah, FL) flow cytometer equipped with a Coherent (Worcester, MA) argon ion laser operating at 300 mW at 488 nm. All tumor samples contained diploid inflammatory and stromal cells, which served as an internal diploid standard as previously described.[27] The high voltage to the photomultiplier tube was adjusted so that the GIGO peak of the diploid cells was located in channel 50 of 256 total channels. Nondiploid populations were defined by the presence of discrete GIGO populations differing from diploid by at least 10%. The DNA index for nondiploid populations was calculated as the quotient of the channel of the nondiploid peak divided by the channel of the diploid peak.

Statistical Methods

The relationship between FCM results and conventional prognostic factors was made using the chi square test. Life table analyses were then performed and survival curves were calculated, using the method of Kaplan and Meier.[28] The entire population, as well as the populations grouped according to the various prognostic factors, was studied. The log rank test was used to determine if significant differences existed between these curves.[29] A multivariate analysis of prognostic factors was performed, based on the rank regression procedure described by Kalbleisch and Prentice.[30] Tumor thickness was used as the stratification variable.

Results

Flow Cytometry

Of the 177 patients initially selected, 15 were eliminated because of technical difficulty. Four of these had very low nuclear counts (<5000) after tissue preparation. Eleven samples with apparently adequate nuclear counts nevertheless yielded uninterpretable DNA histograms, defined as having no peak with a coefficient of variation less than 10%. Thus, interpretable histograms were obtained from 162 (92%) samples, even though many of the lesions were very small and some were more than 10 years old. Of the 162 samples with satisfactory histograms, 124 were diploid, 35 aneuploid, and three tetraploid (Fig. 1). The three tetraploid tumors were excluded from further analysis because of their small number and unclear relationship to melanomas with diploid or aneuploid DNA content, leaving 159 tumors for analysis.

Correlation Between DNA Content and Conventional Prognostic Variables

DNA content was compared to conventional prognostic variables including tumor thickness, Clark's level, ulceration, vertical growth phase, cell type, anatomic location and patient's sex (Table 1). Tumor thickness was significantly related to aneuploidy ($p < 0.005$). While five of 61 tumors less than 1.5 mm were aneuploid (8%), 15 of 38 lesions greater than 3.0 mm thick contained an aneuploid cell population (39%). Similarly, the association between aneuploidy and increasing Clark's level was significant ($p < 0.005$). Ulcerated lesions were more likely to be aneuploid than nonulcerated lesions ($p < 0.005$). The presence of a vertical growth phase was associated significantly with aneuploidy ($p = 0.02$). The association between DNA content and radial growth pattern (superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma) was not significant. The association between DNA content and cell type was significant if epithelioid cell types were compared to all other cell types combined ($p < 0.05$). No significant relationship between ploidy and mitotic index was found. Unexpectedly, head, neck, and trunk melanomas had a significantly lower incidence of aneuploidy when compared to extremity melanomas ($p = 0.005$). No significant relationship between DNA aneuploidy and patient sex was found.

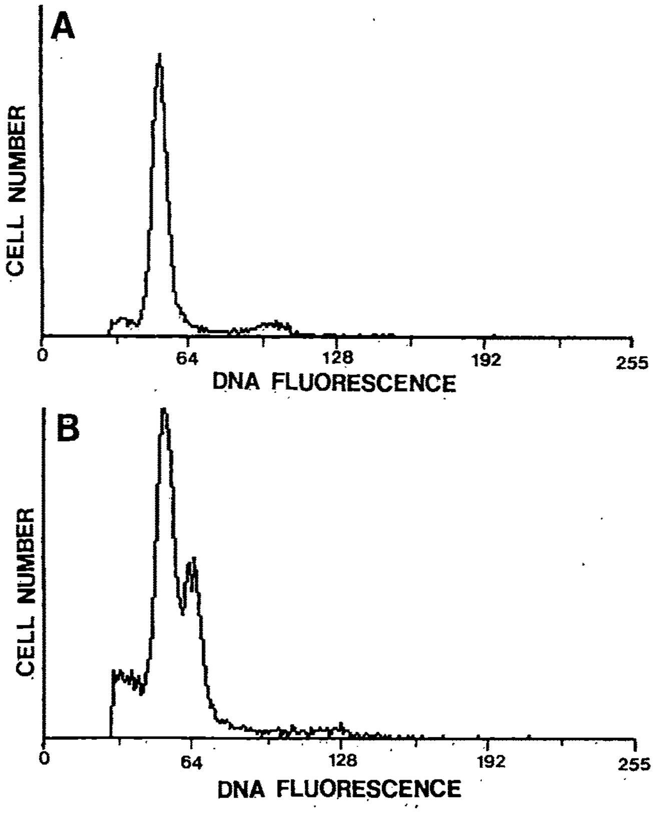
TABLE 1. *Correlation Between DNA Content* and Conventional Prognostic Variables*

Variable	Total No. of Patients	No. of Diploid (%)	No. of Aneuploid (%)	P Value
Thickness (mm)				
<1.5	61	56 (92)	5 (8)	<0.005
1.5–2.9	60	45 (75)	15 (25)	
≥3.0	38	23 (61)	15 (39)	
Level				
I, II, III	72	64 (89)	8 (11)	<0.005
IV, V	87	60 (69)	27 (31)	
Ulceration†				
Absent	84	75 (89)	9 (11)	<0.005
Present	74	48 (65)	26 (35)	
Vertical growth†				
Absent	16	16 (100)	0 (0)	0.02
Present	134	99 (74)	35 (26)	
Cell type†				
Epithelioid	90	75 (83)	15 (17)	<0.05
Other (nevus, spindle, pleomorphic, spindle pleomorphic, spindle desmoplastic, spindle epithelioid)	67	47 (70)	20 (30)	
Location‡				
Head, neck, trunk	73	64 (88)	9 (12)	<0.005
Extremity	81	55 (68)	26 (32)	
Sex				
Male	73	58 (79)	15 (21)	NS
Female	86	66 (77)	20 (23)	

* Nuclear suspensions were prepared from paraffin-embedded melanomas, stained with propidium iodide, and analyzed by FCM; three tetraploid tumors were eliminated leaving 159 for analysis.

† Technically poor histology slides made these determinations impossible in several cases.

‡ Location could not be determined from clinical records in five cases.



FIGS. 1A and B. Sample histograms from diploid (*A*) and aneuploid (*B*) cutaneous melanomas. Diploid cells fall in channel 50. DNA content is given in arbitrary units on 256 channel scale.

Relationship of Disease-free Survival with Ploidy and Other Prognostic Factors

Adequate follow-up documentation was obtained in 145 patients. The mean follow-up time was 4.04 years

TABLE 2. *Relationship of Disease-free Survival with Ploidy and Other Prognostic Factors*

Variable	No. of Patients	Disease-free Survival* 3-year (%)	Disease-free Survival* 5-year (%)	P Value (Log Rank Test)†
DNA content				
Aneuploid	33	35.0	23.3	<0.0001
Diploid	112	77.4	75.5	
Thickness (mm)				
<1.50	57	85.4	80.6	<0.0001
1.5–2.9	55	64.7	57.1	
≥3.0	33	35.5	25.7	
Level				
I, II, III	66	85.3	82.2	<0.001
IV, V	79	54.4	41.8	
Ulceration				
Absent	77	82.0	77.5	<0.001
Present	65	52.5	39.5	
Vertical growth				
Absent	15	100.0	100.0	<0.007
Present	121	63.3	53.5	
Cell type				
Epithelioid	82	83.2	69.5	<0.001
Other	61	46.8	44.2	
Location				
Head/neck	18	54.4	29.0	
Trunk	46	71.7	63.0	NS
Upper extremity	27	78.5	78.5	
Lower extremity	49	65.6	58.8	
Sex				
Male	66	62.4	56.7	NS
Female	79	72.6	61.3	

* Life table analysis was performed and disease-free survival curves were calculated using the method of Kaplan and Meier.

† Differences in survival curves for each variable were compared using the log rank test.

with a range of follow-up between 0.17 and 23.05 years. Within this group of patients, there were 95 documented recurrences and 50 patients who remained recurrence-free. Of the patients without recurrence, the range of follow-up was 0.17–23.05 years. This follow-up included three patients who died without evidence of disease at 0.19, 2.17, and 4.02 years after diagnosis.

The 33 patients with aneuploid tumors had a significantly higher incidence of recurrence and a significantly decreased 3- and 5-year disease-free survival time than the patients with diploid tumors ($p < 0.0001$, Table 2, Fig. 2). Increasing tumor thickness was similarly associated with a significant increase in recurrence rate and decreased disease-free survival time ($p < 0.0001$, Table 2). Increasing Clark's level, the presence of ulceration, the presence of vertical growth phase, and a cell type other than epithelioid were also associated with decreased disease-free survival (Table 2). Anatomic site, patient sex, or growth pattern were not associated with significant differences in disease-free survival.

Association of Disease-free Survival Stratified by DNA Content and Tumor Thickness

For melanomas < 1.5 mm thick, aneuploid tumors had a significantly increased recurrence rate and decreased disease-free survival when compared to diploid tumors ($p < 0.0001$, Figs. 3A and 4). For tumors 1.5–2.9 mm thick, the 5-year recurrence rate for aneuploid tumors was 63% compared to 36% for diploid tumors. However, the disease-free survival curves were not significantly different ($p = 0.247$, Figs. 3B and 4). Aneuploid tumors ≥3 mm had a 100% 5-year recurrence rate compared to 54% for their diploid counterparts. In this group the difference between disease-free survival curves was significant ($p = 0.031$, Figs. 3C and 4).

Multivariate Analysis

A multivariate analysis of prognostic factors based on the rank regression procedure described by Klableisch and Prentice[30] was obtained after stratification for tumor thickness (Table 3). DNA aneuploidy was found to be the most significant unfavorable prognostic factor after adjustment for thickness ($p = 0.002$). DNA content was followed by cell type (favorable characteristic; epithelioid, nevus, or spindle; $p = 0.022$) and vertical growth phase (favorable characteristic; no vertical growth; $p = 0.024$).

Discussion

Assessment of biologic potential in melanomas of the skin is an important and difficult problem in clinical oncology and pathology. The difficulty arises because of the great variability in the clinical course of apparently similar malignant melanomas.[23]

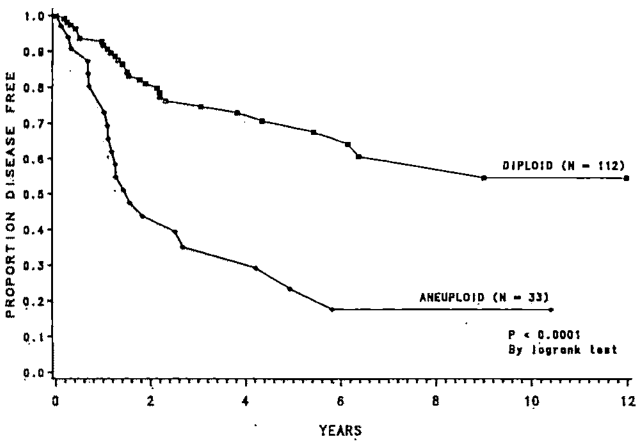
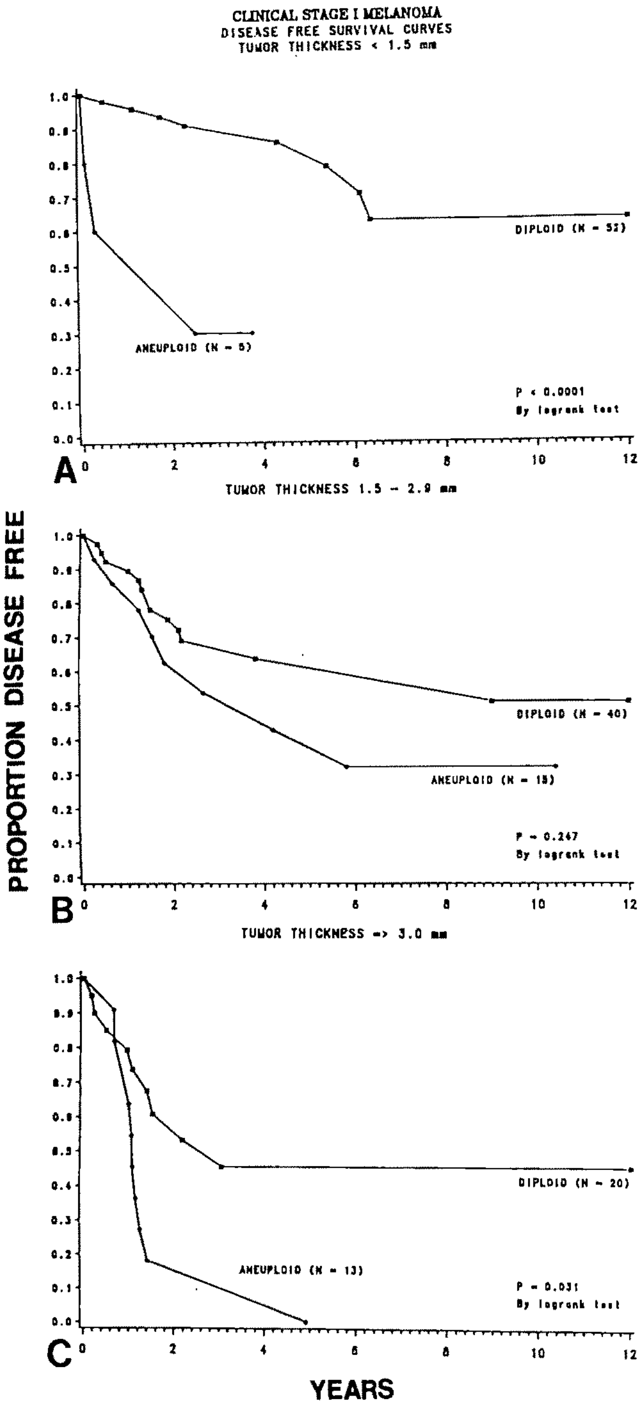


FIG. 2. Actuarial disease-free survival curves for 145 Stage I melanoma patients subdivided by DNA content (aneuploid *vs.* diploid). A significant difference in survival between the curves was found using the log rank test. The number of patients in each group is shown in parentheses.

As a result of prognostic studies in patients with Stage I melanoma, there is general agreement that measuring lesion thickness (microstaging) is the single most important prognostic indicator.[6,11] Except for the most superficial lesions, patients with histologically similar lesions often experience vastly different clinical outcomes. This can make decisions about appropriate therapy difficult and subjective.[11,23,31] Clinical reports using thickness as a guide to determine the use of elective lymph node dissection present conflicting results, further underscoring the fact that present prognostic techniques may be inadequate.[32-35] Clearly what is needed is the establishment of reproducible criteria reflecting the potential of the tumor cells to invade and metastasize, presumably to be used in addition to the existing staging and microstaging criteria.



FIGS. 3A–C. Actuarial disease-free survival curves calculated for Stage I melanoma patients subdivided by tumor thickness (*A*. Tumors < 1.5 mm. *B*. Tumors 1.5–2.9 mm. *C*. Tumors > 3 mm.), and grouped according to DNA content (diploid *vs*. aneuploid). The log rank test was used to compare survival curves within each thickness subdivision. The number of patients in each group is shown in parentheses. DNA content (aneuploidy) significantly influenced disease-free survival for tumors < 1.5 mm and ≥ 3 mm.

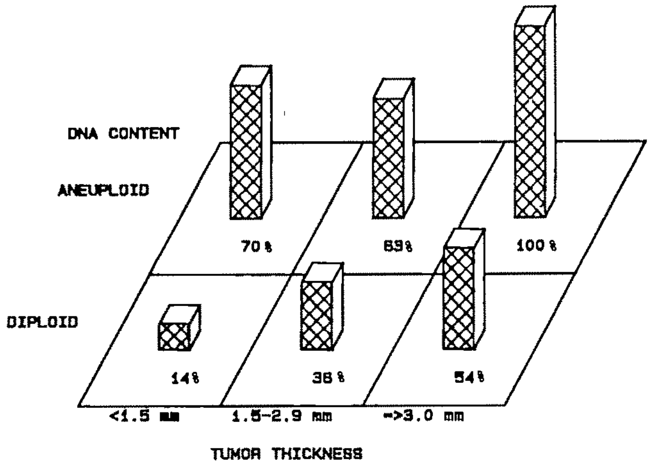


FIG. 4. Three-dimensional graph comparing 5-year recurrence rate, DNA content, and increasing tumor thickness. Within each thickness subgroup, aneuploid tumors had a higher recurrence rate than their diploid counterparts.

TABLE 3. *Multivariate Analysis of Prognostic Factors**

Factor	Chi Square (Log Rank Test)	P Value†	Favorable Characteristics
DNA content (adjusted for thickness)	9.7	0.002	Diploid
Cell type (adjusted for thickness and DNA content)	5.2	0.022	One of the following types: epithelioid, nevus, or spindle
Vertical Growth (Adjusted for thickness, DNA content, and cell type)	5.1	0.024	No vertical growth

* This analysis was based on the rank regression procedure described by Kalbeisch and Prentice.

† After stratification for tumor thickness, DNA content was found to be the most significant prognostic factor (with diploid being the favorable characteristic) followed by cell type and vertical growth.

The need for an improved prognostic system has led to the proposal of numerous histopathologic factors as additional prognostic guides. These include the presence of vertical growth phase, ulceration, number of mitoses, lymphocytic response, cell type, regression, and pigmentation.[5,20–24] None of these factors has been completely satisfactory. First, many of these factors are not significant independent prognostic predictors when tumor thickness is taken into account.[23] Second, assessment of some of these factors is subjective and qualitative, contributing to the persistent controversy surrounding their relative importance and practical value.[23]

Because of the limitations of subjective morphology for assessing the biologic potential of tumors, objective quantitative methods may yield important additional information. Quantitative DNA analysis has been performed on relatively large numbers of specimens from several solid tumors.[14] These studies have established that an abnormal DNA content, (DNA aneuploidy), is significantly related to the biologic potential of several tumors, including cancers of the colon, urinary bladder, prostate, and ovary.[13–15,36–40] The precise clinical value of these studies is still under study and can vary widely for different tumors.

Previously reported data on melanoma from our laboratory[16–18] and others[31,41,42] indicate a strong association between DNA aneuploidy and unfavorable clinical outcome. Our application of FCM to the study of melanoma was greatly facilitated by the development of the capability to recover intact tumor cell nuclei from paraffin blocks. This technique has allowed us to study a relatively high proportion of thin diploid lesions compared to previous studies where difficulty in obtaining adequate fresh tissue limited the analysis to thicker lesions. The reliability of this technique has been documented by Hedley, its originator,[24] and confirmed by others including ourselves.[25] The successful application to small specimens (such as cutaneous melanoma) may be related to our modification of Hedley's original technique, namely, appending a detergent-trypsin nuclear isolation technique to the acid pepsin technique of Hedley. This impression is based on observing the suspensions microscopically before and after the detergent-trypsin step; an increased yield of nuclei and fewer aggregates were routinely observed after this step.

The present study has revealed significant new information. First, it focused upon a large, unique population of patients with Stage I lesions and adequate clinical follow-up (mean: >4 years). Second, it examined the significance of DNA content on disease-free survival as a single factor and demonstrated the relationship of DNA aneuploidy with other unfavorable prognostic factors and shorter disease-free survival. Third, it examined the relative value of DNA aneuploidy compared with other important prognostic factors in a multivariate regression analysis stratified for tumor thickness. This multivariate analysis of prognostic factors demonstrated DNA content to be the most significant predictor of survival after thickness. Most importantly, it demonstrated that aneuploidy can be used to prognostically subclassify melanoma patients with lesions of defined thickness.

The ability to identify patients with thin (<1.5 mm) melanomas at relatively high risk for recurrence seems particularly important since these patients might be candidates for special treatment modalities. Conversely, patients in this thickness category (particularly those 0.76–1.5 mm) with diploid tumors could be reassured that their outlook was relatively favorable. The significant substratification results for the patients with thick lesions (>3.0 mm) also appear important for interpreting results of new adjuvant therapy approaches. Regardless of the thickness stratification used, these data demonstrate that aneuploid tumors are associated with a higher recurrence rate and decreased disease-free survival than their diploid counterparts. That this difference was not statistically significant for lesions 1.5–2.9 mm thick is due to the relatively small numbers of patients in this group.

These findings are strongly suggestive that measuring DNA content can significantly contribute to assessing the prognosis of a given melanoma and that study of paraffin-embedded tissue can allow evaluation of previously inaccessible thin melanomas. However, there are several limitations associated with the present study. First, the percentage of aneuploid tumors relative to the entire study population is low (22%) compared with the 54–85% incidence reported elsewhere.[31,41,42] We believe this discrepancy is largely due to differences in the patient populations studied, as we have described in detail in an earlier report.[17] Unlike previous series, our population consisted entirely of primary Stage 1 lesions, many of which were also low microstage (thickness). However, the possibility exists that we may have underdetected aneuploidy on these small samples of paraffin-embedded material. This issue will only be resolved with improved technology for ploidy determination in paraffin-embedded material because other workable approaches to studying DNA abnormalities in large numbers of small, thin melanomas do not yet exist to our knowledge. Second, the tumors were collected from three institutions over a 20-year period and the influence of variable treatment approaches, as a function of both the institution of origin and the passage of time, on clinical outcome, cannot be quantified.

Regardless of the limitations of this study, the likelihood that analytic techniques will be of benefit in the assessment of cutaneous melanomas appears established.

Acknowledgments

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Effect of Moderate Hypothermia in the Treatment of Canine Hemorrhagic Shock

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This study evaluated a possible protective and therapeutic effect of moderate hypothermia in the treatment of severe hemorrhagic shock. A modified Wiggers shock preparation was used. Normothermic dogs (Group I, N = 6) were maintained at normal body temperature throughout hemorrhagic shock and resuscitation. In Group II, hypothermia was initiated after 15 minutes of hemorrhagic shock (N = 12) and maintained for 60 minutes after fluid resuscitation. Animals were then rewarmed with Group IIA (N = 7) receiving sodium bicarbonate to correct acidosis, while Group IIB (N = 5) did not; all dogs were studied for an additional 120 minutes. During shock heart rate was lower in both hypothermic groups (IIA and IIB) compared to normothermic dogs (85.0 ± 3.9, 77.7 ± 4.6 *vs.* 136.7 ± 4.2, respectively, $p < 0.05$), while +dP/dt (mmHg/s) remained stable in all dogs. Furthermore, pH was lower in the hypothermic (Groups IIA and IIB) compared to normothermic animals at this time period (Group IIA: 7.19 ± 0.02, Group IIB: 7.13 ± 0.02 *vs.* Group I: 7.24 ± 0.02). Arterial pCO_2 was higher in the hypothermic hemorrhagic shock Groups IIA and IIB compared to normothermic group (34.5 ± 2.2, 37.4 ± 2.2 *vs.* 20.3 ± 20, 3 ± 2.0, $p < 0.05$) due to hypothermia-depressed respiration. A higher myocardial O_2 consumption and a negative myocardial lactate balance occurred in the normothermic animals during hemorrhagic shock. After resuscitation and rewarming, stroke volume (mL/beat) and cardiac output (L/min) were lower in hypothermic animals with persistent acid–base derangements (12.6 ± 2.5, 1.3 ± 3.0, respectively) compared to hypothermic dogs with acid–base correction (20.1 ± 3.3, 2.2 ± 0.3) and normothermic dogs (24.6 ± 3.0, 3.0 ± 0.3, $p < 0.05$), while myocardial O_2 extraction and myocardial lactate production were higher. Results suggest hypothermia decreases the metabolic needs and maintains myocardial contractile function in hemorrhagic shock. Hypothermia may have a beneficial effect and, with normalization of acid–base balance, a therapeutic role in hemorrhagic shock.

THE EFFECT of hypothermia in the treatment of hemorrhagic shock is controversial. Hypothermia, which decreases total body oxygen consumption,[1] has been shown to increase survival rate[2] and prolong the period of tolerance to severe hemorrhage.[3] The disciplines of neurologic and cardiovascular surgery have utilized hypothermia during surgical procedures and described a protective effect.[4,5] However, the therapeutic value of hypothermia in the shock state is much less clear, and conflicting data regarding any beneficial effect of hypothermia have been attributed to differences in experimental preparation, type and degree of shock produced, as well as the level of hypothermia achieved.[6-9] The present study was designed to evaluate the effect of moderate hypothermia on cardiovascular function, regional blood flow, and oxygen consumption in hypothermia plus severe hemorrhagic shock.

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Materials and Methods

Hemodynamic Studies

Eighteen mongrel dogs of either sex, weighing between 16 and 28 kg were included in the study. Anesthesia was induced with sodium thiopental (15 mg/kg, I.V.) and maintained with alpha-chloralose in polyethylene glycol 200 (50 mg/kg, I.V.). Dogs were intubated and allowed to breathe room air spontaneously. Polyethylene catheters were placed in the femoral and brachial arteries and advanced into the descending aorta for removal of blood during hemorrhage, blood sampling, and measuring arterial blood pressure. Arterial blood pressure was monitored with a strain gauge transducer (Statham, Model 231D). Polyethylene femoral venous catheters were also placed and advanced into the inferior vena cava for administration of fluids, drugs, and the return of shed blood. Left ventricular pressure was obtained from a Millar catheter (Millar, Inc., Houston,

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Texas) inserted through the left internal carotid artery. The Millar transducer was initially zeroed and calibrated in a 37 C water bath (Millar, Inc., Model PC470). A polyethylene catheter was also placed into the coronary sinus through the right internal jugular vein, and a Swan-Ganz catheter was placed into the pulmonary outflow tract, through the left internal jugular vein. These three catheters were placed under the aid of fluoroscopy. A derivative computer (Hewlett-Packard, Model 8814A, Richardson, TX) provided continuous monitoring of maximal rate of left ventricular pressure rise (+dP/dt) and fall (−dP/dt). All hemodynamic parameters were recorded on a Mingograf recorder (Siemens, Model 81, Grand Prairie, TX). Cardiac output was determined in duplicate by the dye dilution technique using indocyanine green. In addition to the vascular catheters, four peritoneal dialysis catheters (Travenol Laboratories, Model 2C4105, Deerfield, IL) were placed in the ventral midline region of the animals. These catheters were introduced intraperitoneally via an open technique. This involved visualization of the parietal peritoneum before placement of the four catheters. All dogs were heparinized (100 units/kg) immediately before insertion of the left ventricular catheter (Fig. 1).

Coronary Blood Flow and Myocardial Oxygen Consumption

Regional blood flow was measured by injection of 1 × 10^6 microspheres (15 ± 3 μm) as a bolus into the left ventricle (3M Company, St. Paul, MN; New England Nuclear, Boston, MA). Immediately before each injection, the vial containing the microsphere (^{113}SN, ^{57}Co, ^{46}SC, ^{95}Nb, ^{125}I, and ^{85}Sr) was mixed by vortex agitation. One milliliter of the microsphere suspension was rapidly injected into the left ventricle and the catheter was immediately flushed with 10 mL of saline solution. This volume of microsphere-containing suspension allowed for an adequate number of microspheres to be administered (at least 400 microspheres/tissue sample) and ensured accurate measurement of blood flow. Simultaneous with the injection of microspheres and continuing for 120 seconds, reference blood samples were obtained from the femoral arteries, each at a rate of 10 mL/min (Holter pump, Model 911, Critikon, Inc., Tampa, FL). At the end of each experiment, the animals were killed by an overdose of barbiturates. The heart was removed and placed into a buffered formalin solution. The myocardial tissue and reference blood samples were counted for 5 minutes in a multichannel gamma scintillation spectrometer (Packard, Model 5320, Legona Hills, CA). The remaining internal organs were treated similarly. For each set of samples, vials containing small aliquots of each microsphere were used to determine the energy level setting on the scintillation counter to be used.

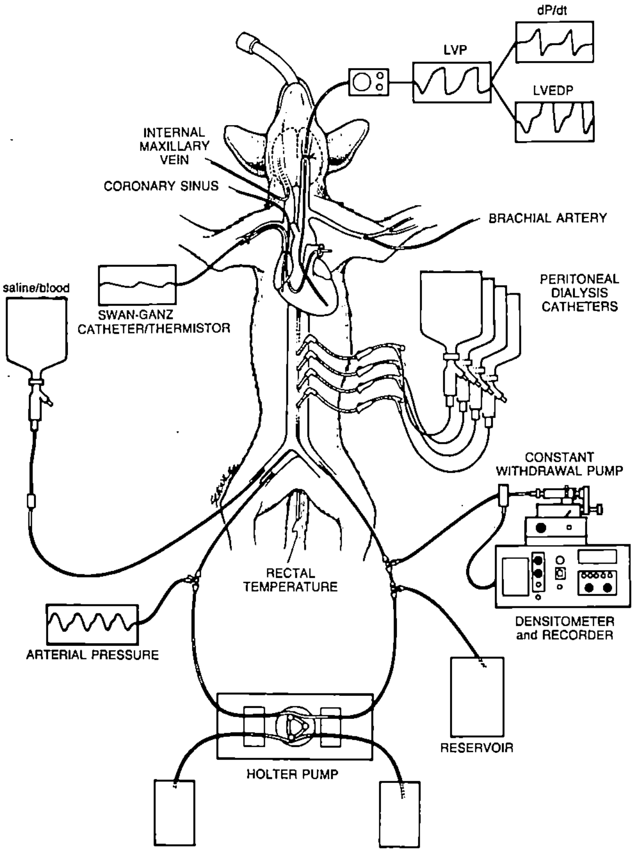

FIG. 1. Experimental model.

From the standards of each microsphere used to set the energy level and the actual sample containing the highest count of microspheres injected, the cross-talk fraction or overlap of gamma energies was calculated for each of the microspheres. The contribution of this overlap of gamma energies of each microsphere was then subtracted and a nuclide reference factor (mL/min/counts) calculated for each microsphere. For each of the samples, the background counts were subtracted and the counts for each isotope were multiplied by the nuclide reference factor in order to obtain a mean blood flow rate.

Hemorrhage, Hypothermia, and Resuscitation

All dogs were given 10 mL/kg of 0.9% normal saline solution during instrumentation. Animals were then allowed to stabilize for 30 minutes. Baseline blood pressure, mean arterial pressure, heart rate, +dP/dt, −dP/dt, left ventricular pressure, left ventricular end-diastolic pressure, pulmonary capillary wedge pressure, pulmonary artery pressure, respiratory rate, urinary output, core body temperature, and rectal (body) temperature (via the Swan-Ganz [American Edwards Laboratories, Santa Ana, CA] catheter thermistor and a rectal temperature probe, respectively) were measured and a micro-

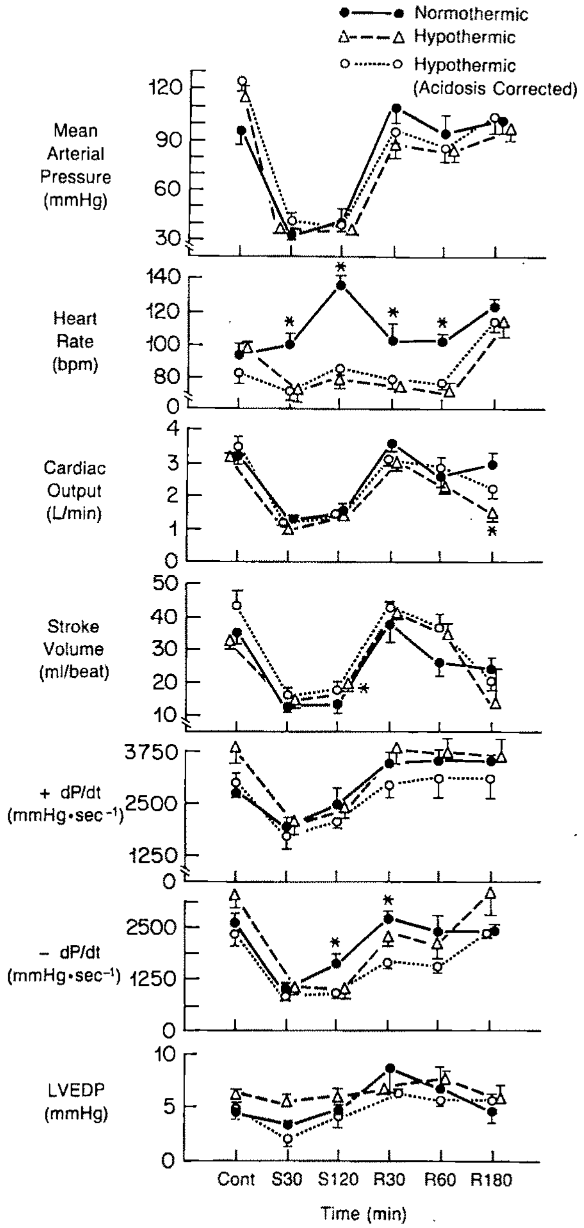

FIG. 2. Hemodynamic and left ventricular contractile response to hemorrhagic shock and hypothermia. All values are given as mean ± SEM. *Significant difference between groups, $p < 0.05$.

sphere was injected for measurement of baseline blood flows. The right femoral artery cannula was then connected to an air-pressure–regulated blood reservoir, and shock was induced, with the end-point being a mean arterial pressure of 35 mmHg. Animals were then divided into three groups. In Group I, six dogs were hemorrhaged over 5 minutes. After 2 hours of controlled hemorrhagic shock, shed blood was returned to all dogs through a micropore filter (Fenwal Laboratories, Model 4C2423, Division of Travenal, Deerfield, IL) via the femoral vein cannula and lactated Ringer's solution was infused (50 mL/kg), with no hypothermic intervention.

In Group II shock was established as described for Group I. Hypothermia was achieved after 5 minutes of hemorrhagic shock by instilling iced normal saline at 4 C into the peritoneal cavity via the peritoneal dialysis catheters. The iced saline was then circulated using a siphon exchange effect to remove the fluid, until a target temperature of 33 C was reached. All measurements, including microsphere flow determinations, were recorded after 30 and 120 minutes of hemorrhagic shock. Two hours after the onset of shock, dogs were resuscitated as described for Group I, and hypothermia was maintained. All measurements were again recorded at 30, 60, and 180 minutes after resuscitation. The animals in Group II were rewarmed 60 minutes after resuscitation, using warmed normal saline solution at 44 C infused through the peritoneal dialysis catheters; then the animals were divided into two subgroups for assessment of hypothermia on acid–base derangements. In Group IIA (N = 7) acidosis was corrected during rewarming using IV sodium bicarbonate titrated to an arterial pH of greater than 7.25. In Group IIB (N = 5) acidosis remained uncorrected. During rewarming animals were given lactated Ringer's solution at a rate of 10 mL/kg/h to keep mean arterial pressure and heart rate at approximate baseline levels.

Statistical Analysis

Results were expressed as mean ± SE. Statistical analysis included an ANOVA and repeated measure procedure (Newman-Keuls). All values were considered significant at $p < 0.05$. All hemodynamic and flow parameters changed significantly from baseline with shock ($p < 0.05$).

Results

Cardiovascular Response

Before shock cardiocirculatory function and metabolic status were similar in all dogs. Hemorrhage to a mean arterial blood pressure of 30 mmHg reduced cardiac output, stroke volume, ±dP/dt, stroke work, and regional blood flows to a similar extent in all animals. Early shock (S15) was characterized by acid–base derangements that included a fall in arterial pH and bicarbonate as well as a rise in circulating lactate levels. Throughout shock, heart rate and respiratory rate were significantly lower in all hypothermic compared to normothermic dogs while mean arterial blood pressure, cardiac output, and left ventricular end-diastolic pressure were similar in the three groups (Fig. 2). Baseline peripheral vascular resistance (mean arterial blood pressure divided by cardiac output and multiplied by 80 to convert units to dyne × s × cm^{-5}) was similar in all dogs (normothermic: 2480 ± 280; hypothermic Group IIA: 2640 ± 244; hypothermic Group IIB: 2880 ± 480). After

120 minutes of shock, the rate of left ventricular relaxation (−dP/dt) was significantly lower in hypothermic Groups IIA and IIB compared to the normothermic shock groups (875 ± 150, 975 ± 200 *vs.* 1550 ± 275 mmHg/s, $p < 0.05$), while the rate of left ventricular pressure rise (+dP/dt), cardiac output, LVEDP, and stroke work were comparable in the three groups at this time. After 2 hours shock, stroke volume was significantly higher ($p < 0.05$) and heart rate lower ($p < 0.05$) in hypothermic compared to normothermic shock dogs.

After fluid resuscitation, but before rewarming, the heart rate remained lower in hypothermic dogs (Group IIA: 75.7 ± 3.8; Group IIB: 70.0 ± 5.4) compared to normothermic dogs (100 ± 4.5 beats/min, $p < 0.05$), while mean arterial blood pressure, peripheral vascular resistance, left ventricular pressure, left ventricular end-diastolic pressure, +dP/dt, and −dP/dt were similar in all dogs during this time. Thirty minutes after fluid resuscitation, cardiac output returned to baseline values but was significantly lower in hypothermic than in the normothermic dogs ($p < 0.05$). Rewarming the hypothermic animals after volume replacement increased cardiac output to a level comparable to that observed in the normothermic animals. Peripheral vascular resistance was higher in all hypothermic compared to normothermic dogs after volume replacement (Group IIA: 3224 ± 240; Group IIB: 3664 ± 280; Normothermic: 2768 ± 300 dyne × s × cm^{-5}; $p < 0.05$). Peripheral blood flows were comparable in all dogs throughout the experimental period, regardless of body temperature (Fig. 3). Adrenal blood flow tended to be lower in both hypothermic groups compared to normothermic dogs after resuscitation, but this difference did not achieve statistical significance.

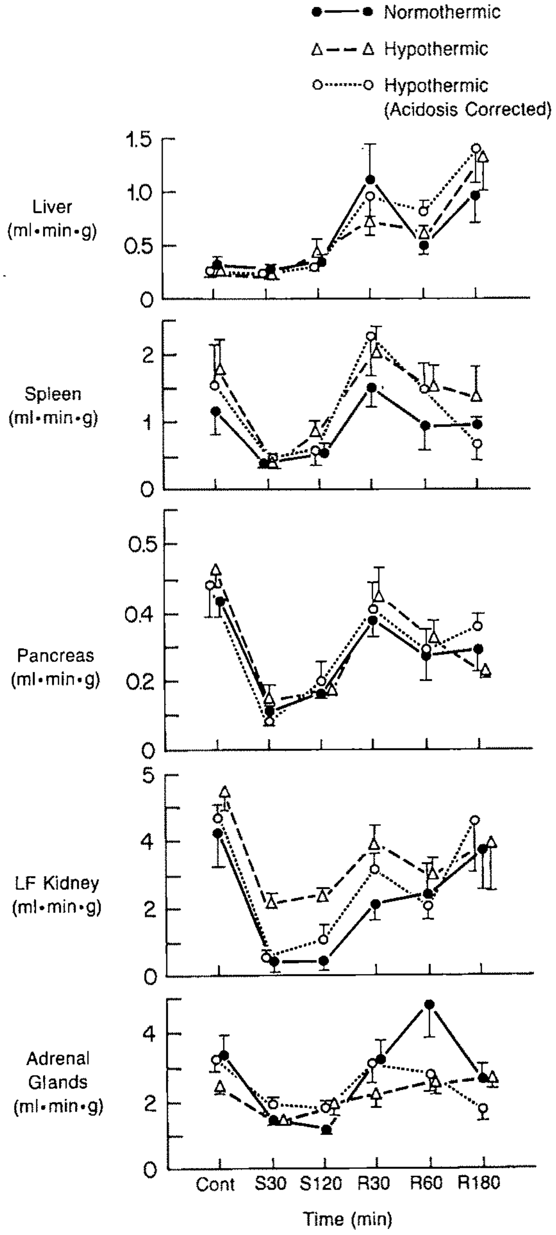

FIG. 3. Changes in regional blood flow during hemorrhagic shock and hypothermia.

Myocardial Blood Flow and Oxygen Metabolism

Baseline myocardial blood flow, myocardial oxygen extraction, myocardial oxygen delivery, and circulating lactate levels were similar in all dogs (Fig. 4). In addition, endocardial-epicardial ratios were similar in all dogs before hemorrhage (normothermic: 1.12 ± 0.06; hypothermic Group IIA: 1.16 ± 0.04, hypothermic Group IIB: 1.09 ± 0.06). There was, however, a tendency toward a higher myocardial oxygen consumption in the normothermic compared to hypothermic shock dogs before shock, but these differences did not achieve statistical difference. Total body oxygen consumption and myocardial oxygen extraction fell during hemorrhagic shock but to a significantly greater extent in the hypothermic dogs, $p < 0.05$. In early shock, myocardial oxygen delivery and myocardial oxygen consumption decreased to a similar extent in all dogs, regardless of body temperature. In late shock endocardial-epicardial flow ratios in normothermic dogs fell significantly from baseline values of 1.12 ± 0.06 to 0.87 ± 0.03, $p < 0.05$. After 2 hours sustained shock, subendocardial perfusion in the hypothermic dogs was unchanged from baseline values and significantly higher in the hypothermic (Group IIA: 1.07 ± 0.05; Group IIB: 0.98 ± 0.04) compared to normothermic dogs (0.87 ± 0.03, $p < 0.05$). In late shock (S120), myocardial blood flow and myocardial oxygen delivery increased to 87% of baseline values in the normothermic shock group but remained significantly lower in hypothermic dogs ($p < 0.05$). After fluid resuscitation, myocardial blood flow and myocardial oxygen delivery increased and myocardial oxygen extraction fell to a similar extent in all dogs. After re-

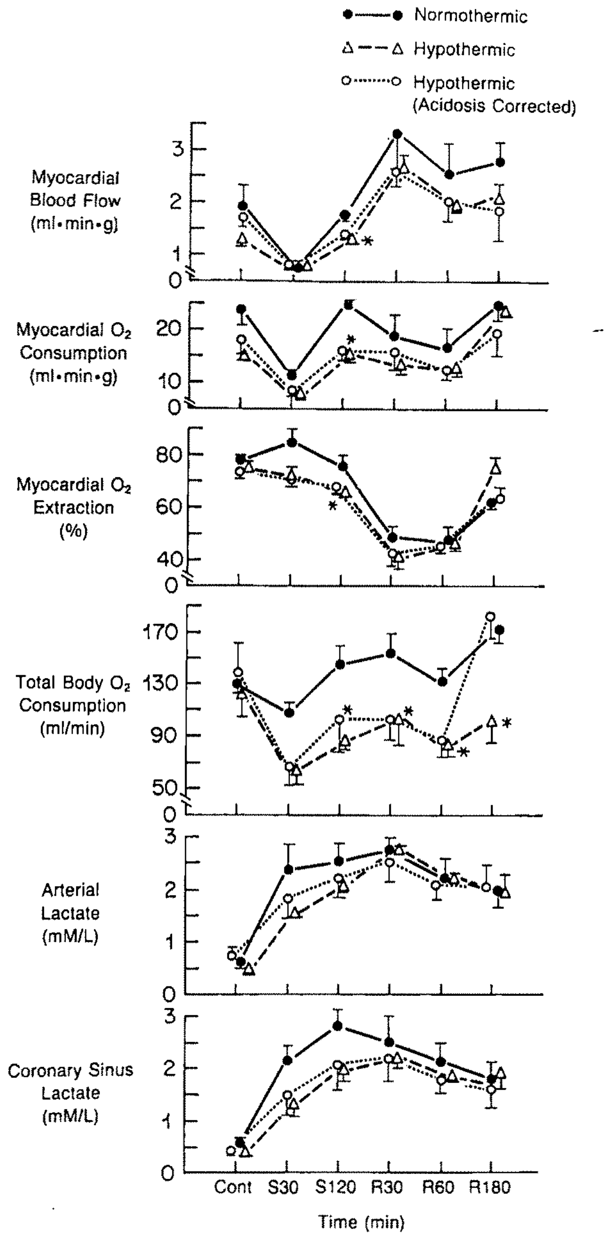

FIG. 4. Coronary blood flow, myocardial oxygen consumption and extraction, total body oxygen consumption, and arterial and coronary sinus lactate levels.

warming (R180) all indices of myocardial perfusion and myocardial oxygen metabolism were similar in the three groups, regardless of body temperature. However, total body oxygen consumption remained significantly lower in those dogs with persistent acid-based derangements ($p < 0.05$).

Acid-Base Status

Baseline measurements of acid-base balance as well as respiratory rate were similar in all dogs (Fig. 5). Hemorrhagic shock caused significant acidosis, as indicated by a progressive rise in circulating lactate levels and a progressive fall in arterial pH and bicarbonate level. While there was considerable variability in arterial pO_2 within groups, the changes from baseline values did not

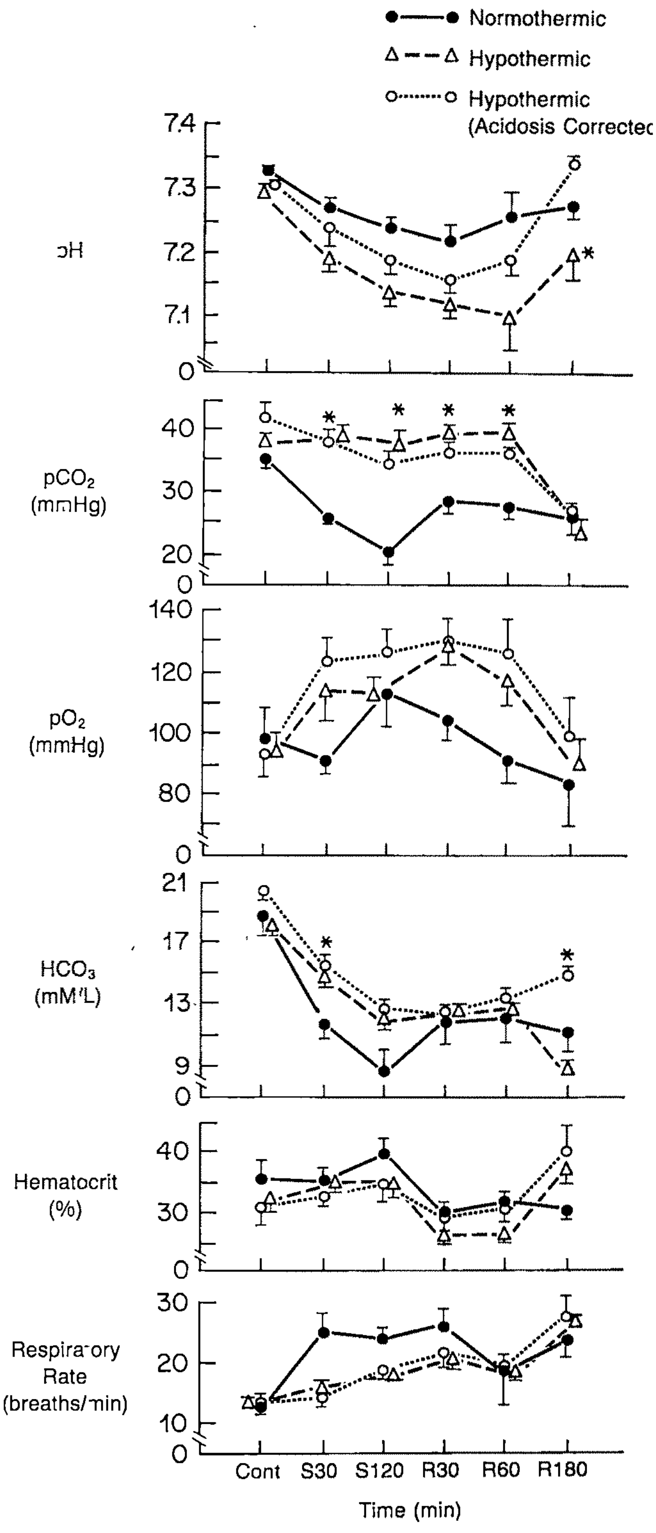

FIG. 5. Acid-base status in hemorrhagic shock and hypothermia.

achieve statistical significance. Hematocrit remained unchanged during hemorrhagic shock in all dogs, and there was similar hemodilution in all groups after fluid resuscitation. Normothermic shock caused a significant tachypnea ($p < 0.05$), producing a fall in arterial pCO_2. In contrast, respiratory rate remained unchanged from baseline values in hypothermic animals, causing arterial pCO_2 to be significantly higher in these dogs throughout hypothermic shock. Immediately after fluid resuscitation (R30), respiratory rate remained significantly lower and arterial pCO_2 higher in all hypothermic compared to normothermic dogs ($p < 0.05$). Sixty minutes after resuscitation, respiratory rates were similar in all groups, and this similarity persisted throughout the experimental study. Acid–base derangements persisted in the hypothermic dogs not given bicarbonate as indicated by a lower arterial pH and serum bicarbonate.

Discussion

Our data showed that moderate hypothermia in severe hemorrhagic shock reduced the metabolic requirements of the heart while maintaining cardiovascular function and myocardial perfusion. The cardiovascular responses to normothermic shock in this study were consistent with those reported previously by this laboratory and by other investigators.[10] These changes included tachycardia, a fall in preload and afterload, impaired left ventricular function, reduced peripheral perfusion, and increased respiratory rate. With crystalloid resuscitation, all cardiocirculatory parameters returned toward baseline values. The induction of hypothermia during hemorrhagic shock produced a significant bradycardia and prevented the tachypnea that is typical of normothermic shock. In addition, hypothermia enhanced left ventricular performance in late shock as indicated by a stable cardiac output and a higher stroke volume despite an unchanged LVEDP and a significant bradycardia. Increased left ventricular ejection, accompanied by no change in cardiac filling or fiber length indicates a positive inotropic response to hypothermia. Our data support the findings of Templeton et al. who showed that hypothermia prolonged the time course of cardiac contraction and increased total tension development.[11] Our data are consistent with studies by Monroe who reported increased ventricular work at a constant LVEDP.[12] Furthermore, Monroe showed no change in left ventricular pressure volume relationships when body temperature was below normal. These data contradict studies by Templeton et al. who described marked alterations in myocardial mechanical properties with changes in temperature, showing that stiffness was inversely proportional to temperature.[11]

Resuscitation improved hemodynamic function in all dogs, but bradycardia and a lower respiratory rate persisted in the hypothermic animals. Thirty minutes after rewarming, cardiovascular function was not significantly different from baseline values, regardless of a previous episode of hypothermia.

The finding of a higher peripheral vascular resistance in the hypothermic dogs 180 minutes after volume replacement and 2 hours after rewarming was an interesting and unexpected finding. Hypothermia may have a prolonged constrictive effect on the peripheral arterial sphincters, an effect not evident earlier in the experiment because of the inherent inaccuracy of peripheral vascular resistance determination during the use of the pressure-controlled hemorrhage reservoir. The authors considered the possibility that a primary fluid deficit may have existed, but this proved unlikely in light of a normal cardiac filling pressure or normal left ventricular end-diastolic pressure. Finally, rewarming likely promoted a massive vasodilatation of the peripheral vascular beds, followed by a vasoconstrictive effort in order to maintain central blood pressure. However, these explanations are purely speculative, and the specific effects of hypothermia on the peripheral vasculature warrants further study.

Myocardial blood flow and oxygen metabolism were comparable in all dogs during early shock, regardless of body temperature. In late hemorrhagic shock, coronary blood flow increased in normothermic dogs, likely due to sympathoadrenal activation, tachycardia, and increased metabolic needs of the myocardium. The lower coronary blood flow in late hemorrhagic shock in the hypothermic dogs supports previous reports that hypothermia decreased myocardial oxygen metabolism and reduced myocardial blood flow.[13,14] Other studies of severe hypothermia (body temperature at 21 C) showed a decrease in cardiac output while subendocardial perfusion was preserved.[15] Studies of normovolemic hypothermia with cardiac output held steady showed a fall in cardiac oxygen consumption and heart rate, an unchanged blood pressure, and a significant increase in the per cent of cardiac output to the heart.[16] Similarly, Sabiston et al. reported that the per cent of cardiac output delivered to the heart increased significantly in hypothermic dogs, attributing the selective increase in coronary flow to a direct effect of temperature on the myocardial smooth muscle and active vasodilitation of the coronary vasculature.[17]

Our data indicate that hypothermia in hemorrhagic shock reduced myocardial oxygen metabolism as indicated by a bradycardia and a lower myocardial oxygen extraction in hypothermic compared to normothermic shock. It was of interest that myocardial oxygen extraction was lower during shock in the hypothermic dogs, despite a higher stroke volume in this group. The metabolic needs of the myocardium are dictated by both contractile function as well as heart rate. However, the pronounced bradycardia in the hypothermic shock apparently overwhelmed the moderate increases in contractile function, decreasing myocardial oxygen requirements. While total myocardial blood flow was lower in late hypothermic shock, there was no evidence of subendocardial ischemia since endocardial epicardial flow ratios remained unchanged from baseline measurements. Our data support the concept that myocardial oxygen requirements are the primary regulator of coronary blood flow, overwhelming any direct effects of temperature on the coronary vasculature.

The acid-base changes observed in normothermic shock are consistent with those previously reported by our laboratory and others. In shock, progressive metabolic acidosis was accompanied by a respiratory alkalosis, preventing excess arterial pH changes despite severe hemorrhagic shock. A metabolic acidosis without respiratory compensation occurred in the hypothermic groups as indicated by the higher pCO_2 and unchanged serum bicarbonate, lower respiratory rate, and higher circulating lactate levels. Our finding of lower coronary sinus and arterial lactate levels in the hypothermic dogs supports a previous study by Shipp et al. who demonstrated that hypothermia reduced lactate formation in the perfused heart.[18] To our knowledge, while no studies have specifically focused on the acid-base status in our model of hemorrhagic shock followed by hypothermia, a large body of literature describes the effect of pH on the hypothermic heart. These previous studies have shown that moderate variations of the extracellular acid-base environment during hypothermia do not impair myocardial function or oxygen demand ratios.[19] While coronary blood flow and myocardial oxygen delivery were lower in late hypothermic compared to late normothermic shock, it is likely that the leftward shift of the oxygen disassociation curve preserved myocardial oxygen consumption and protected cardiac function under conditions of decreased oxygen supply.[20] These data are consistent with previous reports that hypothermia modifies all determinants of oxygen supply but tissue hypoxia does not occur.[19] Several investigators have proposed that intracellular buffering mechanisms compensate for moderate variations in the extracellular pH and that the depressive effects of acid-base disorders on myocardial contractility are related to severe changes in intracellular pH which overwhelm intracellular buffering mechanisms.[20,21] Studies by Poole-Wilson and Langer,[21] using a hypothermic isolated perfused papillary muscle preparation, observed that acidosis was associated with the rapid fall in myocardial tension development while alkaline pH preserved contractile function in a hypothermic preparation. Becker et al.[22] also showed improved cardiac function in hypothermia if pH was adjusted to an alkaline range, attributing enhanced cardiac performance during hypothermia with pH correction to a more ideal biochemical environment for continued aerobic metabolism. It is likely that the inotropic effect of hypothermia in our study would have been significantly enhanced if acid-based correction and ventilatory support had been instituted during the shock period. This hypothesis is supported by the significant increase in cardiac output with acid-base correction in the hypothermic dogs.

Intracellular acidosis may explain the elevated hematocrit at the end of the experimental period. An appropriate pH is necessary to stabilize the Gibbs-Donnan ratio and red blood cell volume while intracellular acidosis leads to cellular swelling.[23] Other possibilities include fluid deficits, increased viscosity, or decreased blood volume secondary to hypothermia itself.[16] Furthermore, an increased circulating catecholamine level secondary to hypothermia may promote splenic contraction and, therefore, hemoconcentration as seen in our experiment.[24] The cause is likely multifactorial.

While the authors acknowledge several problems inherent in studying hemorrhagic shock complicated by hypothermia, this situation is a difficult clinical issue that needs to be addressed. First, it is difficult to separate the physiologic response to hypothermia from the responses to hemorrhagic shock. Moreover, it is likely the hypothermia-mediated increases in ventricular stiffness[1] impair accurate measurement of contractile changes that relate stroke volume to left ventricular filling pressures. Also, in our model difficulties arose in distinguishing the effects of shock-induced acidosis from the effects of hypothermia-induced acidosis. Are these additive detriments or mutually exclusive insults? Could the combination of increased contractile function and decreased peripheral metabolic rate present in the hypothermic shock portend a lesser degree of coagulopathy than that which occurs in normothermic shock? In summary, our data suggest that hypothermia reduces metabolic requirements during hemorrhagic shock while maintaining cardiovascular function and adequate myocardial oxygen delivery. The application of these findings combined with critical attention to the optimal acid-base balance may suggest a potential role of hypothermia in the treatment of severe hemorrhagic shock.

Acknowledgment

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Septic Necrosis of the Midline Wound in Postoperative Peritonitis

Successful Management by Debridement, Myocutaneous Advancement, and Primary Skin Closure

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Wound management following laparotomy for postoperative peritonitis and varying degrees of parietal necrosis remains a challenging and controversial problem. Because maintained peritoneal integrity and primary wound closure offer the best opportunity for survival, an original technique involving bilateral incisions to relax skin and rectus fascia is proposed. This technique permits medial myocutaneous advancement and primary tension-free skin closure of midline laparotomy incisions. Sixty-nine patients with severe postoperative peritonitis were treated according from 1980 through 1985. Nine of these patients died of advanced multiple organ failure soon after referral, and eight more died after prolonged treatment. Fourteen patients had one or more reoperations for complications. Only nine wound failures resulted, including five eviscerations and four wound infections followed by progressive dehiscence. The bilateral relaxing incisions healed secondarily without complication. Survivors developed midline wound hernia; ten of the 52 surviving patients have had these repaired. This method of primary closure is safe when performed in conjunction with rigorous surgical care of intraperitoneal infection and may enhance survival. We recommend the technique to surgeons who treat severe postoperative peritonitis and septic necrosis of midline laparotomy wounds.

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CLOSURE of the abdominal wall adds to the already formidable challenge facing the surgeon when parietal necrosis and dehiscence or evisceration complicate severe postoperative peritonitis. Because primary closure under tension in these critically ill patients often fails, alternative methods of abdominal closure have been proposed. These techniques include open wound management with delayed closure or grafting; prosthetic fascial closure with Silastic® sheeting (Dow Corning Corporation Medical Products, Midland, MI); Marlex® (C. R. Bard, Billerica, MA); polypropylene or Vicryl® mesh (Ethicon, Somerville, NJ); and more complex closures using pedicled or rotation flaps. Although these methods have been performed safely, certain disadvantages inherent in each technique require departure from the ideal: primary tension-free parietal closure without use of prosthetic material.

Achievement of this ideal implies satisfactory treatment of the underlying problem. Residual septic foci and enteric fistula would defer convalescence and probably contribute to a higher mortality rate in these seriously compromised patients. Both the incidence of complications and of early reoperations directly related to the technique should be low. Multiple procedures prolong recovery and add risks; ideally, staged closure, removal of prosthetic material, grafting, or repair of incisional hernia would be avoided.

Since 1965 the Intensive Care Unit of the Department of Surgery at Hôpital Saint-Antoine, Paris, has been

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dedicated to managing severe septic abdominal conditions and has become an international referral center, admitting patients from France, Western Europe, and Africa. From 1970 through 1985, we managed 590 cases of postoperative peritonitis. We use the term postoperative peritonitis to designate diffuse suppuration (free or multiloculated fluid) or a solitary abscess in direct relation to a high-output gastrointestinal (GI) fistula. The classification excludes solitary abscesses unrelated to a leak in the GI tract. Of the 590 cases of postoperative peritonitis, conventional fascial closure was achieved without excessive tension in 329 (55%). In the remaining cases, we used alternative means of wound management; these techniques have evolved as we sought to lower our rates of complications and repeat operations. From 1970 through 1977, we accomplished closure using through-and-through retention sutures (in 120 cases); otherwise, the abdomen was left open (in 14 cases). In 1977, one of us (E.L.) suggested a method involving lateral skin and fascial relaxation incisions and advancement closure of the midline wound. From 1977 through 1985, we refined this technique of tension-free closure in 127 cases. We report our experience from 1980 through 1985 when the laparotomy wounds of 69 patients (representing 41% of the postoperative peritonitis cases) were managed by bilateral myocutaneous advancement and primary midline skin closure.

Patients and Methods

All patients were seen in the Centre de Chirurgie Digestive of Hôpital Saint-Antoine, Paris, France. The average age was 46 years (range: 13–78 years). Nine patients were older than 70 years. Forty-seven men and twenty-two women were included.

Sixty-eight patients were transferred from other centers, and one patient received initial treatment in our department. Sixty-two patients (90%) had two or more laparotomies before referral. Fourteen (20%) had already had repeat operations in an attempt to control postoperative sepsis and were referred for treatment of persisting infection. In all 69 patients, sepsis complicated a direct procedure on the GI tract (Table 1). In nearly all cases, postoperative peritonitis was caused by technical complications or errors.

Peritonitis was generalized in 62 patients and localized in seven patients. The initial incision was midline in all patients. The abdominal wall had dehisced in 16 patients and was infected or necrotic in 25. Thirty-six patients (52%) presented with three or more of the following severity indicators in addition to the peritonitis: septicemia, shock, adult respiratory distress syndrome (ARDS), renal insufficiency, hepatic insufficiency, thromboembolism, GI hemorrhage, more than three operations, radiotherapy, and substantial parietal necrosis (Table 2). The mean number of severity indicators cumulative by patient was 2.7 ± 1.7. Fourteen patients had associated disease at the time of their first operation. The mean interval between initial operation and reoperation was 17 days and was more than 5 days in 90% of patients.

TABLE 1. *Preexisting Conditions in 69 Patients* Prior to Operation Using Wound Closure Technique*

Origin of postoperative peritonitis	
Upper GI tract	21
Small bowel	33
Appendix	4
Colon	11
Cause of postoperative peritonitis	
Anastomotic leak	45
Bowel necrosis	13
Surgical trauma	11

* Associated disease (N = 14): alcoholism in two, obesity in one, heart disease in five, Crohn's disease in one, and miscellaneous in five patients.

Technique

Our protocol for treatment of postoperative peritonitis[1] was rigorously followed and includes the following elements: (1) complete exposure of the abdominal cavity through a long midline incision. Thorough exploration, (often a lengthy procedure) requires patience, gentleness, and perseverance despite the frequent difficulties encountered during dissection. (2) meticulous peritoneal toilet consisting of aspiration of all blood, ascitic fluid, pus, succus entericus, and feces. Fibrinopurulent exudate was gently debrided using moist gauze; any densely adherent fibrinous material that could not thus be removed was left in situ. Peritoneal lavage with saline was used only to clear debris, and no adjuvant antibacterial substances were instilled into the abdominal cavity. (3) absolute avoidance of intestinal suture or anastomosis. Every breach of intestinal continuity, including those inadvertently created during exploration, is exteri-

TABLE 2. *Preexisting Severity Factors in 69 Patients**

Septicemia	32
Shock	20
ARDS	26
Renal insufficiency	21
Hepatic insufficiency	19
Thromboembolism	5
GI hemorrhage	11
≥3 previous laparotomies	31
Radiotherapy	3
Extensive parietal necrosis	16
None	8

* Severity factors (N = 69): 1 in 16, 2 in 9, 3 in 12, 4 in 13, 5 in 6, 6 in 3, and 7 in 2 patients.

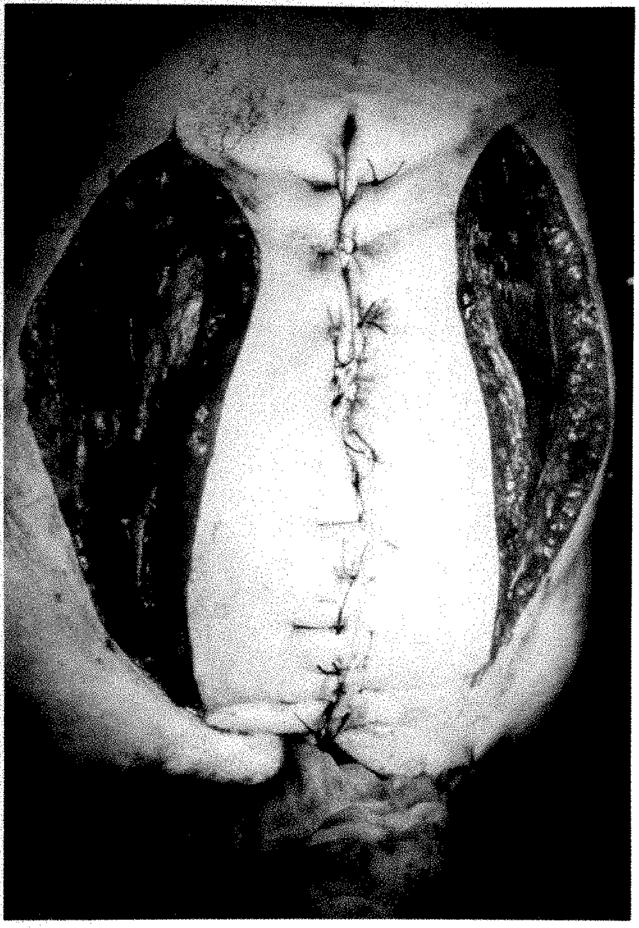


FIG. 1. Mikulicz pack in lower portion of midline wound.

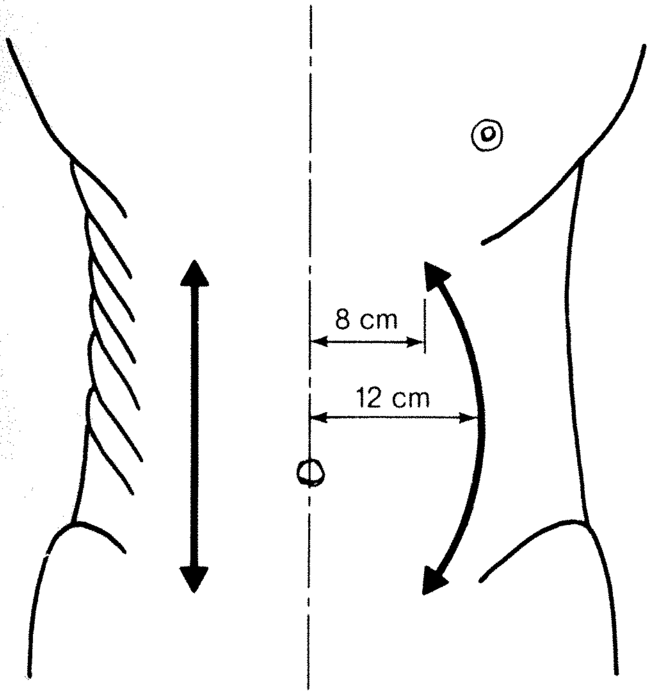
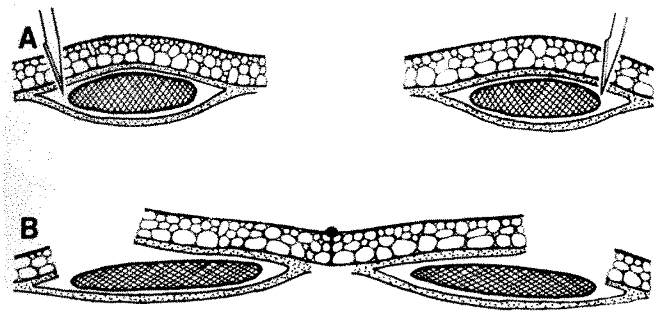


FIG. 2. Relaxation incisions.

orized (N = 38). Stomas thus created are designated salvage in our institution and include loop jejunostomy, loop ileostomy, or loop colostomy if the opening is small; otherwise, end-stoma and mucous fistulas are created.[1] Limited segments of intestine with multiple openings are resected. Any immobile segment such as the duodenum is intubated with silicone catheters held by a pursestring suture, then isolated from the peritoneum by corrugated drains and a Mikulicz pack.[2] Concomitant procedures included salvage enterostomy in 38 patients, intubation and intraluminal irrigation in 25, drainage alone in one, and others in five. (4) active drainage of all dependent areas, accomplished using large perforated silicone catheters surrounded by corrugated rubber drains. These drains were thus routinely placed in subphrenic, subhepatic, and bilateral paracolonic gutters. We provided capillary drainage of the pelvis with Mikulicz packs (Fig. 1).[3] Other Mikulicz packs were placed within large abcess cavities (54 in the pelvic area, 17 in the upper abdomen, and two elsewhere). All Mikulicz packs were left in place for 12–14 days. (5) associated procedures: gastrostomy (N = 36)) or, in the case of gastrectomy or discontinuity of the duodenum, Witzel jejunostomy (N = 16). The gastrostomy was initially used for drainage or hemostatic irrigations, then for enteral nutrition. Jejunostomies were used solely for enteral nutrition.[4] (6) abdominal wall management: bilateral myocutaneous advancement and primary midline skin closure. After debridement, we provided medial mobilization of the margins of the primary incision by making long counterincisions along the lateral edge of the crural arcade from the costal margin superiorly to the suprapubic area inferiorly. The skin and subcutaneum are incised in a curvilinear fashion, and the anterior sheath is incised in a linear manner approximately 1 cm medial to the lateral edge along its entire length (Fig. 2). This is more easily accomplished if the surgeon can palpate the rectus border from within the abdominal cavity. The transverse insertions of the rectus muscle to the anterior sheath must be carefully separated medially as far as feasible. After it is dissected, this unit of anterior sheath, subcutaneum, and skin can then be advanced medially for various distances because the rectus muscle splays as the mobilization proceeds (Fig. 3). If the abdominal wall is supple, 10 cm or more on either side of the midline can be gained to bridge the defect (Fig. 4). If the abdominal wall is indurated, less mobilization is possible.

After excision of any midline necrotic debris, we close the skin using nonabsorbable monofilament mattress sutures. In the few instances where the aponeurotic layer was of good quality and could be approximated without tension, it was closed using running sutures of O-Dexon® (Davis and Geck, Wayne, NJ). The skin and



FIGS. 3A and B. Transverse section. *A.* Skin and aponeurotic relaxation incisions. *B.* Dissection of anterior sheath from rectus muscle.

subcutaneum should be minimally dissected at the margin of the midline incision; otherwise, the subfascial plane could be inadvertently entered, creating a free bipedicled flap (Fig. 5). If a stoma is already present at the time of repeat operation and would interfere with the performance of the relaxation incision, the stoma is relocated. The relaxation incision would then be extended from the stoma site. If the posterior sheath is inadvertently lacerated, we suture the defect and interpose Vicryl mesh between the viscera and the abdominal wall (Fig. 6). These wide relaxation wounds are covered with petrolatum-saturated gauze. Closure by secondary intention proceeds and is usually complete within 5 to 9 weeks (Fig. 7); skin grafts are not necessary.

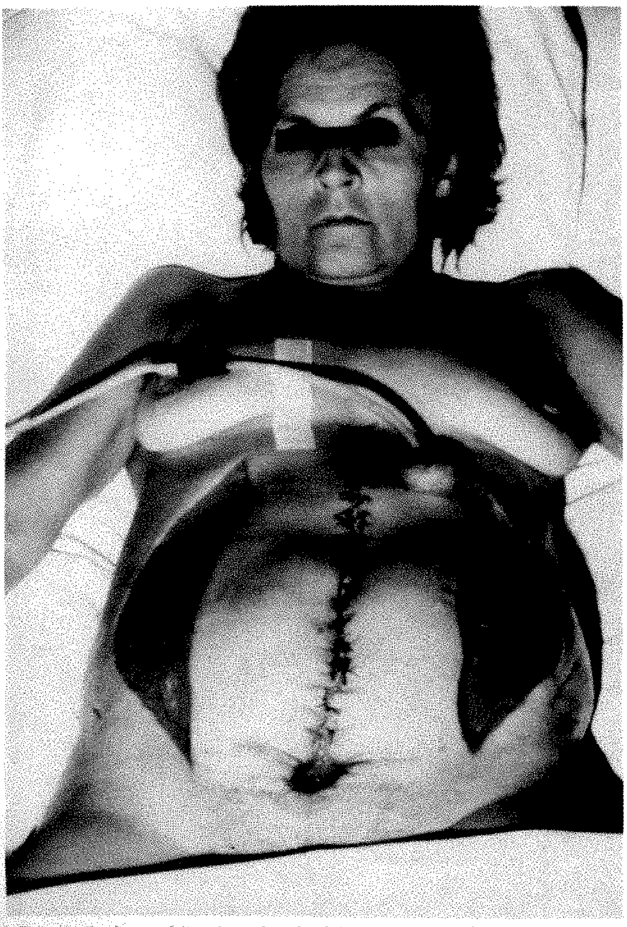
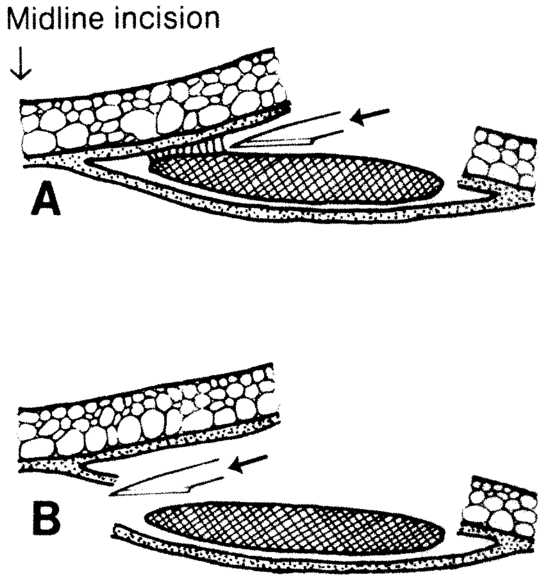
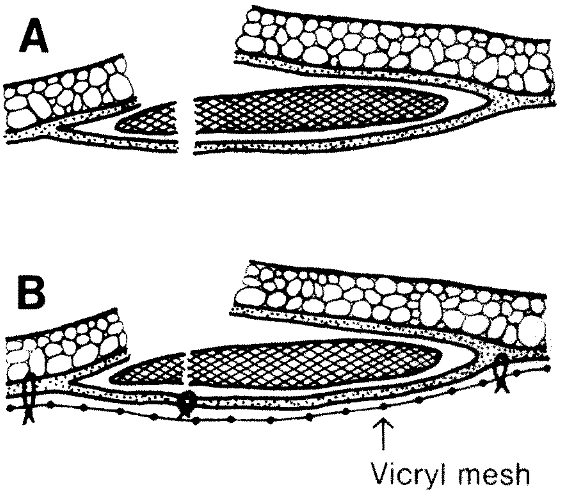


FIG. 4. Patient with relaxation incisions 15 days after operation.



FIGS. 5A and B. *A.* Flap dissection. *B.* Flap dissection extended too far.

Because many of these patients require elevation of stomas or loops of intestine, certain principles have evolved to direct stoma placement. We always create the stomas after completing the relaxation incisions and after debriding the midline wound. We try not to place them within the bed of the relaxation incision, preferring to place them either lateral to the wound or in the isthmus medially; nevertheless, we occasionally must bring the mucous fistula through the rectus muscle and



FIGS. 6A and B. *A.* Inadvertent laceration of posterior sheath. *B.* Repair by Vicryl® mesh.

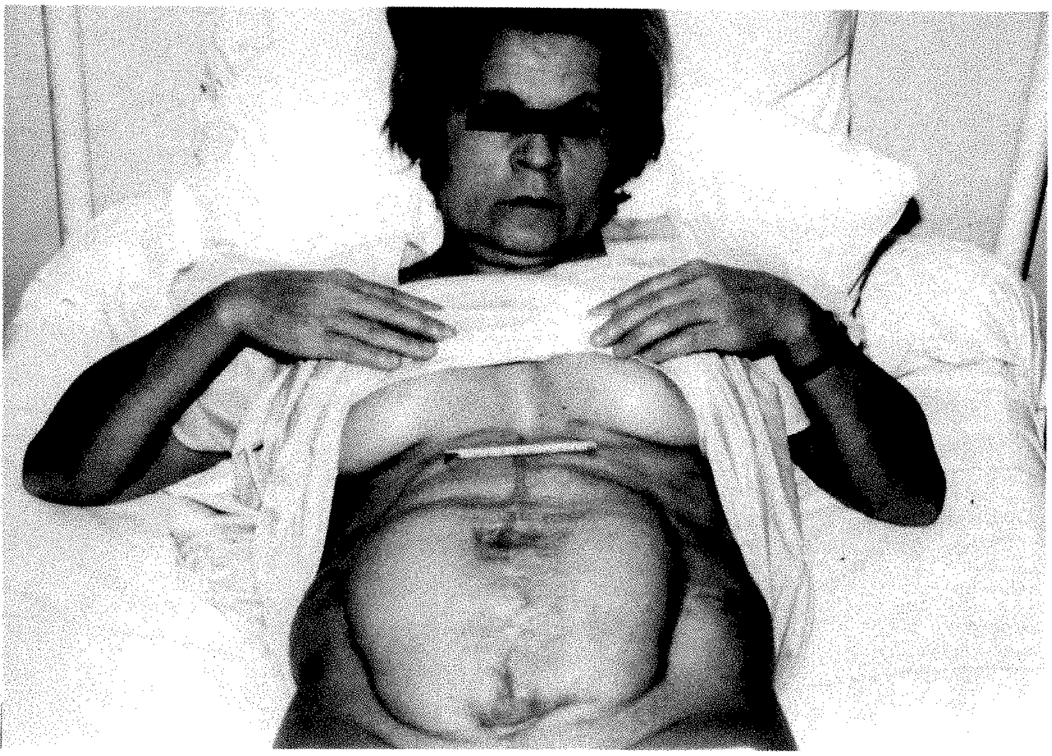


FIG. 7. Photograph of same patient as in Figure 4 shows healing after 9 weeks.

accept the greater complexity of postoperative wound care. We now routinely drain the pelvis with a Mikulicz pack through the inferior extremity of the midline incision.[3] Any other drains are brought through the flanks in a dependent position; these orifices are invariably made lateral to the counterincisions (Fig. 8).

All patients were treated aggressively in the intensive care unit by a team of intensive-care specialists. Blood loss, fluid and electrolyte imbalances, and acid-base disturbances were corrected. We routinely gave prophylaxis against upper GI hemorrhage, thromboembolism, and decubitus.[5,6] Total parenteral nutrition was continued or initiated within 48 hours. Nutritional support was gradually converted to the enteral route whenever effective peristalsis resumed.

Results

Seventeen patients died (24.6%), among whom were nine moribund patients who had been referred in an advanced state of multiple organ failure and who died within 10 days after admission. Mean hospital stay, including repeat hospitalization for reestablishment of GI continuity, was 74 days (range: 1–180 days); for survivors, mean hospital stay was 88 days (range: 20–180 days).

Assisted ventilation was discontinued within 7 days after operation in 53 patients (77%). The remaining 16 patients required prolonged ventilatory support because of respiratory failure.

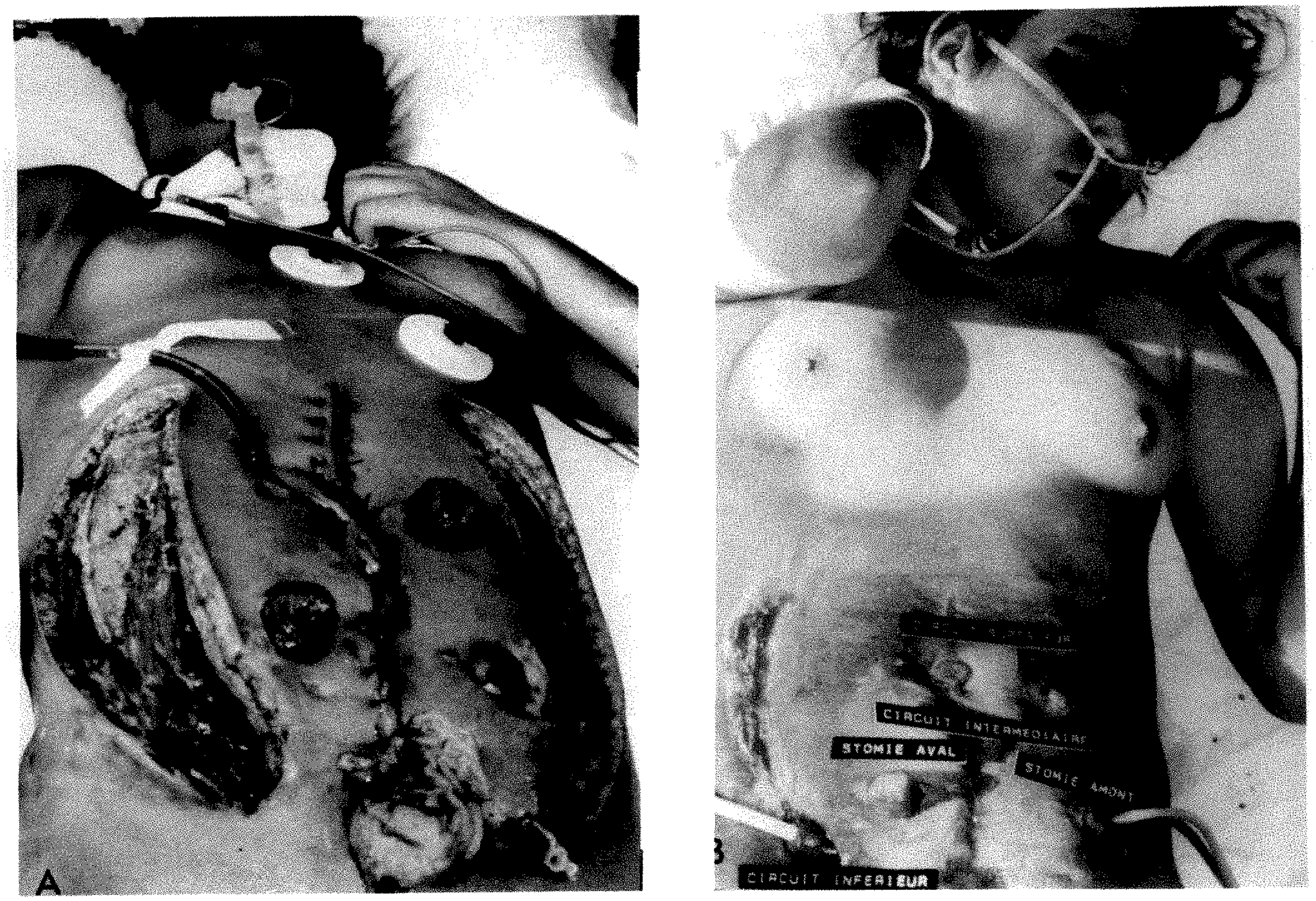
All patients received total parenteral nutrition until effective peristalsis permitted administration of at least maintenance enteral nutrition. We were able to initiate nasoenteric or jejunostomy-tube feeding at a mean of 5.2 days after operation (range: 4–11 days).

Complications

Thirty-three complications of the initial operation (Table 3) required repeat operation in 14 (20%) patients (Table 4). Of the five eviscerations, two with excessive tension were a consequence of improper application of the technique; three others were due to underlying sepsis. Slowly progressive dehiscence in four cases occurred during the second postoperative week but did not produce visceral complications since granulation tissue covered the loops as the margins separated.

Exposed intestinal fistulas were not observed. All postoperative fistulas occurred in relation to bowel necrosis or necrotizing pancreatitis; none were due to parietal or suture erosion of a superficial intestinal loop.

We observed nine recurrent abscesses (13%). In two, the abscesses spontaneously drained and the patients recovered without further interventions. Five patients had seven reoperations; of these patients, two survived and three died. Two others died without repeat operation, and their abscesses were found at postmortem examination. Etiology of those residual collections was incomplete exploration (abscess left behind) in one case, GI necrosis or perforation in two cases, and no identifi-



FIGS. 8A and B. Patient with relaxation incisions. *A*. With drains, Mikulicz pack, stomas. *B*. Healed.

able cause in the six remaining cases. Among these six, three were in advanced multiple organ failure—they had more than three severity factors—at the time of referral.

TABLE 3. *Complications*

Complication	No. of Patients (%)
Abdominal wall dehiscence	9 (13)
Evisceration	5
Partial and progressive	4
Enterocutaneous fistulas	9 (13)
Biliary	1
Small bowel	7
Colon	1
Recurrent abscesses	9 (13)
Residual abscesses	1
Abscesses due to GI nerosis or perforation	2
No evident cause	6
Intra-abdominal hemorrhage	3 (4.5)
Small bowel obstruction	1 (1.4)
Extradigestive complication	2 (2.8)
Totals	33

Late Results

One patient died of metastasis from the original cancer, and one died of complications following enterostomy closure. Of the 50 survivors, 35 had received stomas; 30 had GI continuity restored, and five had end ileostomy or colostomy and could not have closure because of local or general contraindications. These elective repeat operations were generally done through the midline laparotomy incision, although a few patients with loop stomas needed only peristomal circumcisions for closure. Only four patients had concomitant repair

TABLE 4. *Reoperation for Complications*

Reason	No. of Reoperations	Deaths
Recurrent abscess	7*	3
Intra-abdominal hemorrhage	3	1
Small bowel obstruction	1	0
Evisceration	1	1
Extradigestive complication	2	1

* Five patients.

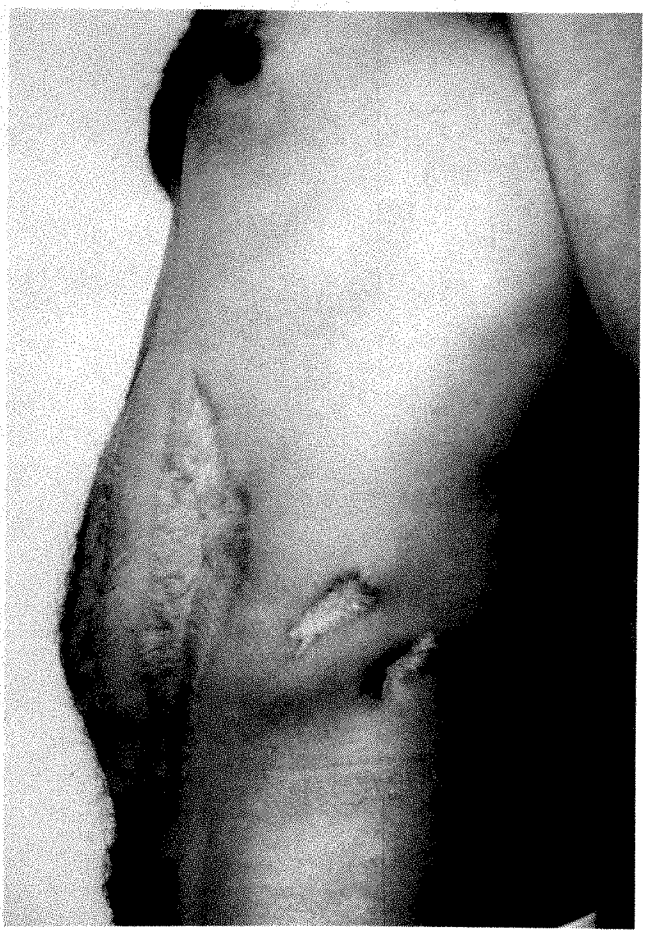


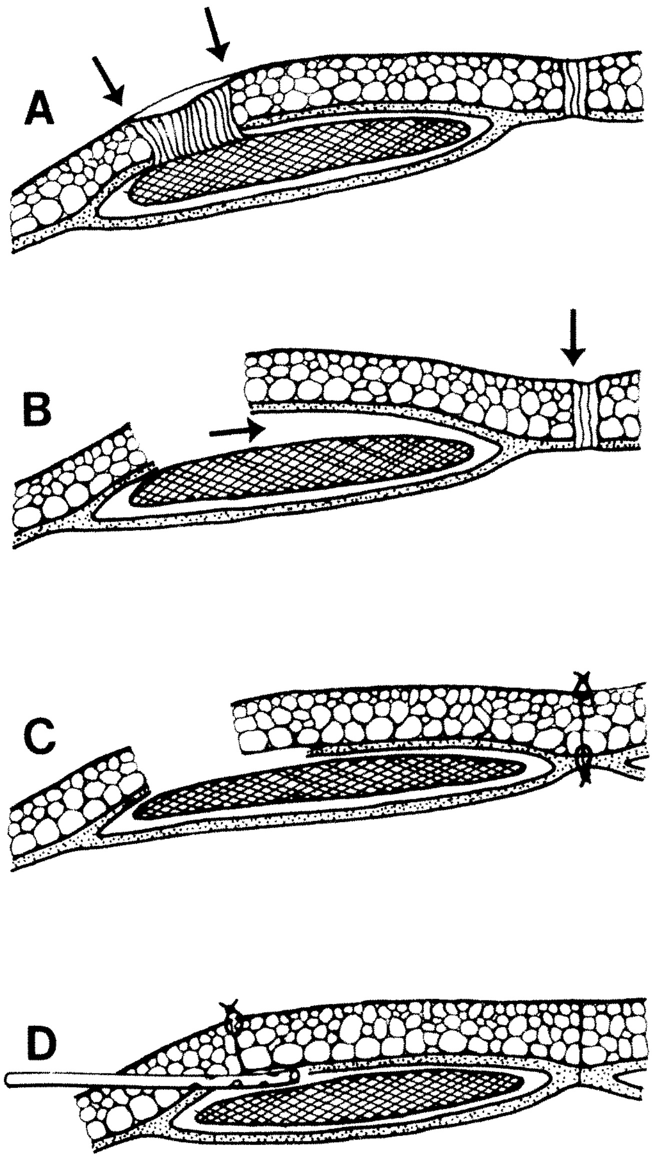
FIG. 9. Photograph shows major incisional hernia.

of midline incisional hernia at the time of restoration of GI continuity. No prosthetic material was used during closure since the margins were simply freshened and approximated. These reoperations were usually delayed for 2–3 months after resolution of the septic event. In all cases, dissection between the advancement flaps and the viscera was easy and bloodless.

Because only the skin is closed during the definitive operation, midline incisional hernia inevitably ensues. This caused major discomfort in 17 patients and aesthetic objections from 31 patients (Fig. 9). No herniation developed through the relaxation incisions. We repaired the incisional hernia in ten patients and needed no prosthetic material. To prevent necrosis of the skin flaps, we avoid dissection between the skin and fascia during herniorrhaphy. In conducting this procedure, we open the midline incision, excise the scar tissue over the relaxation incision, mobilize from the lateral incision by again dissecting between the rectus muscle and anterior sheath, reapproximate the midline fascia, and finally close the skin over the midline and lateral incisions (Fig. 10). If the fascia cannot be approximated without tension, we insert Vicryl mesh beneath the margins and suture it to the posterior aspect of the abdominal wall. Necrosis of a portion or all of the flap complicated three cases; these were simply debrided, and secondary closure proceeded without incident.

Discussion

We have modified our treatment of postoperative peritonitis over the past 10 years as our experience broadened. As a consequence of early recognition of well-established clinical signs,[5] rapid diagnosis followed



FIGS. 10A–D. Technique of repair for incisional hernia. *A.* Step 1: excision of scar tissue (bilateral). *B.* Step 2: dissection of anterior sheath from rectus muscle. *C.* Step 3: midline fascia repair and skin closure. *D.* Step 4: skin closure of lateral incisions over closed wound suction catheter.

TABLE 5. *Comparative Planned Reexploration Results*

Wound Closure Technique	Patients	Postoperative Peritonitis (%)	Death (%)	Exposed Fistula (%)	Total Stay (days)	ICU Stay (days)	No. of Recurrent Abscesses (%)
Polyurethane[13]	9	100	67	11	—	—	2 (22)
Polyurethane[14]	34	61	61	—	—	—	—
Polyurethane[15]	32	100	56	6	48	—	7 (22)
Polyurethane[16]	16	—	25	19	150	—	1 (6)
Gauze[17]	14	14	7	7	—	—	2 (14)
Gauze[18]	18	—	39	28	130	54	6 (33)
Gauze[19]	13	61	15	7	—	—	4 (30)
Gauze[20]	20	50	60	—	67	—	10 (50)
Gauze[21]	100	—	50	—	—	—	—
Gauze[22]	18	94	23	5.5	120	—	6 (33)
Zipper[23]	61	44	25	—	—	40	6 (12)
Marlex®[24]	16	—	28	—	—	—	—
Total	352	—	(41.7)	(7.7)	(94)	(433)	44/187 (23.5)

by careful application of evolving surgical principles,[1,2,7,8] aggressive intensive care, and nutritional support, overall mortality rate has consistently decreased from 48% before 1980 to 17% from 1980 through 1985.[5]

Even as survival has improved, complexity of the referral cases has increased. Most of our cases are now transferred after failure to control sepsis, malnutrition, and multiple organ failure. Initial assessment documents this by an increase in mean number of severity indicators in our overall series of postoperative peritonitis: 0.8 before 1980, 1.8 from 1980 through 1982, and 1.9 from 1983 through 1985.[5] We now reoperate much earlier; whenever there is any evidence of persistent sepsis, we invariably perform thorough exploration of the abdomen. We avoid anastomosis or simple closure of any disruption of GI continuity and exteriorize mobile bowel as end or loop stomas or intubate and isolate any fixed or retroperitoneal viscus that has been injured or broken down. Problems associated with high-output fistulas or stomas have been solved by reinfusing succus entericus, using specially designed equipment.[9]

Although other workers have reported similar therapeutic approaches to problems of the viscera,[10] widely divergent methods are used to deal with parietal inflammation, necrosis, or defects. The state of the abdominal wall is often disastrous; after debridement of the necrotic areas, aponeurotic closure may be impossible. Moreover, with the edema and distension of the viscera, even the intact abdominal wall often cannot be closed without unacceptable tension. Closure under any tension using such methods as through-and-through retention sutures or sutures over dental rolls aggravates parietal ischemia, may erode the underlying viscera, and risks delayed dehiscence and evisceration (often complicated by exposed fistulas).[11] Given this alternative, many therapeutic techniques have been proposed.

Leaving the abdomen open in an attempt to facilitate drainage of persistent or recurrent collections is an intuitively attractive approach but has little physiologic benefit. The exposed peritoneal surfaces weep large amounts of fluid and often manage to seal septic foci beneath, thus mandating secondary explorations.[12] Protection of the intestinal loops in those cases has been provided by petrolatum-saturated gauze, polyurethane sheets, or moistened gauze,[13–22] and a variation on this therapeutic principle (*i.e.*, planned reexploration) is practiced by those who provide temporary coverage of the viscera by the intact abdominal wall, by prosthetic mesh, or by a zipper (Table 5).[23,24] Routine reexplorations are undertaken at variable intervals, usually 48 hours, and are repeated until gross suppuration resolves.[19,20,23] Improved survival and low incidence of recurrent sepsis reported by those using repeated debridement and lavage is difficult to evaluate since these series include instances of *first-time* peritonitis along with the postoperative peritonitis.[17,19] In series limited to postoperative peritonitis with multiple organ failure, more comparable to our experience at Hôpital Saint-Antoine, significantly improved results have been reported.[13,15,22,23] By carefully applying the surgical principles that have evolved from our experience,[1–4] similar benefit in survival and a low incidence of recurrent sepsis can be obtained without reexploration.

Comparisons among series suffer from difficulties of definition; nevertheless, our rate of recurrent abdominal sepsis is slightly better than that observed in the series advocating repeated reexploration (13% *vs.* an average of 23.5%, Table 4). Prevention of recurrent sepsis depends on the following principles: (1) thorough peritoneal exploration, which minimizes the risk of residual abscesses; (2) diversion of GI injury, leaks, fistulas, or necrosis to prevent suppuration due to recurring leakage; and (3) capillary drainage of the pelvis and large abscess cavities, a technique that we find more effective than using large or multiple suction catheters. Recurrent abscess may occur but should be recognized by ultrasonographic examination[25] or by computed tomography (CT) scan[26] whenever clinical suspicion is high; reexploration or percutaneous drainage may then be more rational. Of the two types of recurrent abscess we report, unexplained and those caused by GI perforation or necrosis, abscess caused by GI perforation or necrosis could not be prevented by a policy of routine reexploration. Rather than a cause, the unexplained abscess may be a manifestation of multiple organ failure (peritoneal failure) since nearly all of ours were found in patients with multiple organ failure at admission. Repeated lavage in this instance could only have a local effect. This hypothesis is illustrated by the example of patients managed by routine reexploration who have persistent gross suppuration until death.[20] The hypothesis is supported by the fact that no technique of reexploration prevents recurrent abscess. Among the practical complications caused by repeated operation are prolonged ventilator dependence, ileus, decubitus, total parenteral nutrition, lengthier stay in the intensive care unit, and high cost. Exposed fistulas complicated a mean of 8% of the cases in the reviewed series (Table 4) regardless of the method used for wound protection. These fistulas are associated with a 40% death rate and require at least a prolonged stay in the intensive care unit.[11] We used the open abdomen technique at Hôpital Saint-Antoine from 1971 through 1977[11] (when conventional closure was impossible) but abandoned it in favor of the method of wound management we report here. The open technique has been rejected by others,[27] including those who initially preferred the approach or restricted it to exceptional cases.[28]

Ogilvie[29] first proposed the use of prosthetic cotton-mesh closure of large abdominal wounds during World War II. Similar management with synthetic materials such as polypropylene and Marlex continues to be reported.[25,30-33] Presence of the mesh minimizes external trauma to the superficial loops, but the rate of exposed fistulas remains high, ranging between 6% and 16%. Recurrence of peritoneal sepsis varies from 15% to 66%.[31,34] Late complications such as mesh extrusion, bowel fistula, and difficulty in mesh removal have led some authors to favor coverage of the defect with split-thickness skin grafts[31] or myocutaneous flaps.[25,31,34]

Levasseur et al.[35] used Vicryl mesh to close the fascia in 17 patients. The material was applied during the first intervention in seven patients and during the initial reoperation in the other ten patients. Two enterocutaneous fistulas and three residual abscesses complicated the method among this group. This material is well tolerated (especially in a septic milieu), does not harm the viscera, and carries no risk of rejection. Although late herniation is inevitable, it may be repaired. Use of Vicryl does not completely prevent development of exposed fistulas. We reserve Vicryl mesh for exceptional cases of massive abdominal wall loss when closure is impossible despite relaxation incisions.

Conclusion

We present a simple, straightforward method of parietal closure: debridement of necrotic tissue, bilateral relaxing incisions, adequate muscular effacement, and tension-free skin closure. Since peritoneal integrity and defenses are maintained, postoperative care is simplified. In contrast to the open technique, fluid losses are minimized, and patients need not be kept in bed with assisted ventilation. Protection of the small bowel permits peristalsis and, therefore, provision of nutrition by the enteral route. Despite the difficulty of comparing series, our confidence in the defense capacity of the peritoneum appears justified; the incidence of residual abscess is scarcely more frequent than that reported with the open method. The late reoperations, which restore GI continuity, are facilitated by primary closure. With the rapid rehabilitation that accompanies clearance of all septic foci, earlier stoma closure and incisional hernia repair can proceed. Dissection beneath intact skin (instead of skin grafts) is simpler and safer.

The technique described should be reserved for the most serious cases of peritonitis. Parietal loss is an essential criterion; however, closure may not be possible in patients with distended and thickened bowels, even in the absence of parietal defects. The greater the number of previous operations and delay between the first operation and initial intervention, the more likely we are to use this method of wound management.

Acknowledgment

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Book Reviews

William P. Longmire, Jr., M.D.
Advisor for Editorial Board
Los Angeles, California

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Advisor for Residents in Surgery
Durham, North Carolina

Surgery for Cerebrovascular Disease. Wesley S. Moore. 957 pp. New York: Churchill Livingstone. 1987. $150.00.

THE TEXTBOOK ENTITLED, *Surgery for Cerebrovascular Disease,* edited by Dr. Wesley S. Moore is a compilation of a large number of noted physicians with expertise in the management of cerebrovascular disease. As stated in the preface of the book, Dr. Moore has accumulated authors from each of the disciplines involved in cerebrovascular surgery. Of particular value in the text is the segment on epidemiology, particularly the chapter authored by Dr. Kace and associates. In this section and the section on clinical considerations, many of the pertinent aspects of atherosclerosis, as manifested by both cerebrovascular disease and lesions at other sites, are brought into perspective. In the section on pathology, popular theories relative to the etiology of transcient ischemic and previously asymptomatic carotid stenoses are advanced by Dr. Luzby.

The section on noninvasive studies has a detailed description of each noninvasive study currently available. The multiplicity of studies reviewed in this section underscore our current lack of standardization of diagnostic evaluations and the rapidly evolving technology in the noninvasive assessment of cerebrovascular disease. Although many methods are reviewed in great detail, the more recent introduction of transcranial Doppler is only briefly mentioned.

The surgical management of lesions of the cerebrovasculature is presented in somewhat repetitious detail, yet presents all available data addressing the respective clinical presentations. Dr. Moore handles the areas of controversy by having advocates of both operative and nonoperative management of lesions present their cases within the text.

This text should provide a complete reference to the current status of surgical management of cerebrovascular disease, with a significant amount of additional data regarding the disease process itself. The depth to which the text manages each of the respective issues is well beyond that of the usual book and is strongly recommended as a reference for the surgical management of this disease. For this reason, it should be a valuable addition to the literature and of significant value to neurologists, neurosurgeons, vascular surgeons, and cardiac surgeons.

RICHARD H. DEAN, M.D.
Winston Salem, North Carolina

Surgical Treatment of Metastatic Cancer. Steven A. Rosenberg. 286 pp. Philadelphia: J.B. Lippincott Co. 1987. $59.50.

THIS TOME is a contribution by active or former staff members of the National Cancer Institute (NCI) for the diagnosis and surgical treatment of metastatic disease to various organ sites. Chapters are organized and devoted to the biologic principles of the metastatic process, and to the diagnosis and surgical resection, with curative intent, of established metastases to the lung, liver, brain, and lymphatics. The editor addresses these organ sites to increase awareness of the value of surgery for the curative treatment of patients with metastases from solid tumors.

This monograph is organized into seven basic chapters that deal with the biology of cancer invasion, diagnosis, and surgical therapy. The introduction is organized to provide the reader with an overview of cancer biology, mechanisms of neoplastic invasion, and metastases. The author deals with the development of the cellular theories and the active process of invasion, and with biochemical mechanisms responsible for tumor cell interaction, membrane alterations with the invasive process, and tumor cell surface receptors. In a succinct fashion, this chapter organizes past and contemporary hypotheses drawn from the vast laboratory and clinical experience available for cancer invasion and metastases. The more recent concepts of angiogenesis and metastases are likewise reviewed with conclusions of experimental immunotherapy of metastases.

The remaining six chapters deal predominantly with the clinical aspects of diagnosis and therapy of metastases of the aforementioned organ sites. Chapters 2 and 3 deal with the diagnosis and surgical therapy of pulmonary metastases. Each chapter is well-organized and comprehensive and is supported with radiographs, figures, and tables, which are complementary to the text. The chapter for resection of pulmonary metastases reviews the extensive experience of the Surgical Branch of the NCI for the management of metastatic soft-tissue sarcomas and osteogenic sarcomas as a component of disease of favorable histologic types. The clinical relevance of this organization distinguishes the less favorable prognosis for head and neck cancer, colorectal carcinoma, uterine-cervical cancer, breast carcinoma, and melanoma.

Chapters devoted to the diagnosis and therapy of hepatic metastases are well-organized, contemporary, and are authored by surgeons experienced in the management of metastatic disease to this organ. The authors place in perspective the organization and interpretation of diagnostic parameters (*e.g.,* liver function tests, radiography, imaging, ultrasonography, computed tomography [CT] and magnetic resonance imaging [MRI]). The section that deals with diagnostic arteriography and venography is abbreviated and is a shortcoming of this chapter. Conversely, the review of hepatic resections is comprehensive, and gives the reader a candid appraisal of clinically applicable approaches for the workup and management of solid tumor metastases to the liver. An extension of this chapter provides insight into endocrine metastases and metastases of noncolorectal, nonendocrine origin, and the end results with hepatic resections for these sites. The chapter concludes with the technical approaches, indications, and results for the various hepatic resections. Both chapters are supported with contemporary, pertinent bibliography.

The chapter that reviews brain metastases is likewise organized to provide the clinician an overview of the incidence, biology, clinical features, neurodiagnostic evaluation, and principles for management of this metastatic site. Also addressed are medical management principles, determinants of radiation therapy responses, and adjunctive therapies available other than surgery. Although this volume is not a text of descriptive techniques, details for contemporary management and operative techniques are enumerated to provide insight for the impact of technical advances in the management of brain metastasis. Survival is addressed with evaluation of the prognostic factors relevant to individual cases (*i.e.*, primary histologic type and performance status). An encyclopedic bibliography is provided for this comprehensive, readable chapter.

The final chapter is dedicated to the treatment of regional lymph node metastases of various histologic types. The diagnostic parameters discussed include lymphangiography, lymphoscintigraphy, and MRI. The author addresses randomized studies that evaluate the efficacy of prophylactic node dissections for extremity melanoma, carcinoma of the oral cavity, and breast carcinoma. These therapeutic dilemmas are succinctly reviewed with the conclusion that no benefit exists for prophylactic nodal dissection, and there appears to be no role for debulking of disease in which effective chemotherapy is available. The merit of this chapter is the comprehensive review of retrospective studies for node dissections of specific tumors in various (19 total) organ sites. While these studies are predominantly retrospective, a review of this therapeutic option has been drawn together in a concise and clear presentation for the efficacy of lymphadenectomy as determined by disease-control rates and actuarial survival.

In summary, this reference textbook is a well-organized, readable, comprehensive tome of clinical value to the surgical oncologist who deals with neoplasms of these various organ sites. Further, it will have broad appeal to the surgical resident and practicing surgeon allowing organization of diagnostic, management, and therapeutic concepts for tumors metastatic to these organs.

KIRBY I. BLAND, M.D.
Gainesville, Florida

Surgical Diseases of the Pancreas. John M. Howard, George L. Jordan, Jr., and Howard A. Reber. 958 pp. Philadelphia: Lea & Febiger. 1987. $145.00.

THE FIRST EDITION of this book by Drs. Howard and Jordan was published in 1960. Since that time, major advances have occurred in the investigation and treatment of pancreatic disorders. Drs. Howard and Jordan are well-known distinguished senior surgeons who have contributed a great deal to pancreatic surgery. Dr. Reber, co-editor, eminently fills the role of the younger surgeon-investigator to add balance to this work, which has evolved into a perfect blend of the scientific, the clinical, and the surgical-technical aspects of pancreatic diseases.

The book clearly represents the end result of a very arduous task. It is well written and the illustrations are good. Historical overviews, basic anatomy and physiology, clinical concepts and controversies, and surgical principles and preferences are all covered in detail and embrace virtually all facets of pancreatic surgery. I would have preferred to have a better balance of the internist's and the invasive radiologist's views, but this does not detract too much from the value of the book since it is written mainly by surgeons and primarily for surgeons. The wide spectrum of pancreatitis as seen in various parts of the world is well delineated by an array of international experts. I predict that this book is going to be a success. Despite some minor deficiencies, I believe that it is destined to become a standard reference for surgeons operating on the pancreas.

A. RAHIM MOOSSA, M.D.
San Diego, California

Letters to the Editor

January 28, 1987

Dear Editor:

I refer to "An Analysis of Survival and Treatment Failure Following Abdominoperineal and Sphincter-saving Resection in Dukes' B and C Rectal Carcinoma."[1] By comparing the effectiveness of abdominoperineal resection and sphincter-saving operations, the authors strongly imply that these operations are interchangeable in the treatment of rectal cancer. Nothing could be further from the truth. Abdominoperineal resections should be reserved for those patients in whom sphincter-salvage is not possible. If sphincter-salvage is attainable, why would one add the perineal portion of the operation to the treatment plan? It appears to me that the logical plan for the treatment of rectal cancer would be clarified from the following algorithm: (1) abdominal exploration to determine the presence or absence of both advanced gross distant metastasis and/or local invasion; (2) a resection of the primary tumor including the proximal lymphatic routes and an appropriate (whatever that is) length of distal cuff below the lesion; (3) abdominoperineal resection if no appropriate distal cuff is attainable; (4) the question of feasibility of an anastomosis (stapled, sewn, pull-through, or colo-anal) if a satisfactory cuff is attainable; (5) anastomosis, if attainable, should be done; and (6) no need to complete the perineal resection if anastomosis is not possible. The cancer operation has been done and a Hartmann procedure with an end sigmoid colostomy is the appropriate operation.

Nowhere in the algorithm is there a choice for performing an abdominoperineal resection for a lesion appropriately conducive to sphincter salvage or vice-versa. The one instance in which anastomosis may be considered for a lesion more amenable to abdominoperineal resection would be when palliation is best served with an anastomosis. Consider, for instance, the patient with liver metastasis in which even a 0.5-cm. cuff may be considered adequate in order to keep the gastrointestinal tract in continuity.

It is true that the choice of operation may also be determined by the technical expertise of the surgeon, by the experience with alternative anastomotic procedures, by the habitus of the patient, and the presence of advanced metastatic disease. Nevertheless, these factors do not in any way allow a general comparison of the efficacy of these procedures for the treatment of rectal cancer.

B. A. PORTIN, M.D.
Buffalo, New York

Reference

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Dear Editor:

Dr. Portin presents an "algorithm" for the treatment of rectal cancer in which he asserts that a sphincter-saving procedure should be performed whenever technically feasible. If the therapeutic formula presented by Dr. Portin had been supported by reliable data, we would agree that our own analysis would not have been necessary. It is precisely because there is considerable controversy relative to the propriety of sphincter-saving operations that our study was performed. Dr. Portin himself underscores this controversy when he suggests that an anterior resection should be performed with "an appropriate (whatever that is) length of distal cuff below the lesion." He further goes on to state that if no appropriate distal cuff is attainable, abdominoperineal resection is necessary and should be performed. In our view, these statements provide justification for our study in that one of its specific aims was to determine the significance of distal margins of resection in sphincter-saving procedures. Our data clearly indicated that treatment failure and survival were not significantly different in patients undergoing sphincter-saving resections whose distal resection margins were <2 cm, 2–2.9 cm, or >3 cm. Further, the number of positive nodes, Dukes' class, and tumor size were not important discriminants in the selection of one operation over the other. This information tends to support Dr. Portin's contention that abdominoperineal resections should be reserved for those patients in whom sphincter-salvage is not possible; however, it is perplexing that he would be comfortable in accepting this approach without the benefit of a well-defined analysis. Perhaps it is Dr. Portin's view that our study was carried out to confirm that which he considered to be self-evident. The fact that we saw fit to perform our study indicates that we disagree with this contention.

NORMAN WOLMARK, M.D.
BERNARD FISHER, M.D.
Pittsburgh, Pennsylvania

August 25, 1987

Dear Editor:

We read with interest the paper of Taylor et al. entitled *Digital Ischemia as a Manifestation of Malignancy.*[1] However, in our view, the omission of several references greatly detracts from this paper's value. In the first place, no mention was made of the series of six cases of digital gangrene associated with neoplasm, which we reported in 1978 in *La Nouvelle Presse Medicale,*[2] a series that is still the largest so far published in this field. *La Nouvelle Presse Medicale* is the most respected French medical journal devoted to internal medicine, and when Eugene Garfield considered which medical journals had the greatest impact,[3] he classified *La Nouvelle Presse Medicale* as 15th in world medical literature and second among the non-English language journals.

Taylor et al.[1] also forgot to include a reference to the work of Kaniak[4] or to a report published in 1985 by Petri et al.[5] Even more surprising was their failure to mention that case n°4 in their series had previously been published.[6]

As a member of the Committee of Directors of the Journal des Maladies Vasculaires, I know how difficult it is to check carefully those parts of papers proposed for publication that concern references. However, this tedious and time-consuming work is important for several reasons: (1) when an important series on the same subject considered is missing, the value of a paper proposed for publication is spuriously increased; (2) some authors try, and sometimes succeed, in publishing their case reports in several journals, which makes it difficult to establish the exact number of cases reported; and (3) the prestige of a journal depends on how often it is referred to in other journals, so that a missing reference is detrimental not only to the authors but to the journal.

Professor Michel Vayssairat
Paris, France

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October 19, 1987

Dear Editor:

We have read with interest the letter from Dr. Vayssairat regarding our paper on the association between digital gangrene and malignancy. Dr. Vayssairat has expressed several concerns that may be ennumerated as follows: (1) We have omitted from our review reference to several previously published papers on this same subject.[1-3] (2) It is Dr. Vayssairat's opinion that our omission of these references detracts from the value of our paper. (3) Our failure to cite the references has detracted from the prestige of the journals in which papers were published.

We acknowledge the omission of the previously published papers from our review of the literature. All authors recognize the difficulty involved in conducting a comprehensive review of the world's literature on any subject due to the profusion of scientific articles and journals currently extant. We specifically recognized and cited this difficulty in our paper. Quoting from the abstract, "to date however we are aware of 23 published case reports of digital gangrene associated with malignancy" and from the body of the paper in which we stated, "to our knowledge there have been 23 published case reports linking digital ischemia and malignant disease" indicates with this specific wording our recognition of the difficulty of compiling a comprehensive literature review. We are pleased to acknowledge the contributions of the other authors and specifically acknowledge that Dr. Vayssairat's case series contained a description of six patients whereas ours described only five, making his series published in Nouvelle Presse Medicale the largest series reported (of which we are aware) in the medical literature.

With regard to Dr. Vayssairat's second contention that our failure to mention these references greatly detracts from our paper's value, we offer the following comment. The purpose of our paper was to inform the reader regarding our experience with, and our opinions about, the association of digital gangrene and malignancy, and was specifically not to establish our primacy or indeed supremacy in this field. We believe the paper's value rests exclusively in its ability to convey information to the reader. Our citation of 41 references in the bibliography provides ample evidence of our desire to recognize the contributions of others to this field.

With regard to Dr. Vayssairat's contention that our failure to cite the listed references detracts from the prestige of the medical journals in which they were published, we comment that the value and prestige of a medical journal is a matter to be decided by the subscribers and the readers thereof. We have never ascribed great significance to the so-called citation index.

Parenthetically, many of us who contribute regularly to the medical literature have frequently encountered reports on subjects regarding which we have also published papers we personally consider of seminal importance, only to find our publications absent from the bibliography of the new work. We do not consider such omissions to reflect anything more than the substantial difficulty involved in compiling a complete list of publications on any subject, especially if one wishes to include articles published in the many languages used by various minorities of the world's scientific community.

Lloyd M. Taylor, M.D.
John M. Porter, M.D.
Portland, Oregon

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2. Kaniak J. Gangrene of peripheral part of extremities in plasmocytoma. Pol Arch Med Wewn 1974; 51:95–101.
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November 18, 1987

Dear Editor:

Silberman reported his experience with clinical stage I melanoma among patients who presented with lesions of Clark levels deep III through V.[1] Only 10% of his patients had positive lymph node dissections. He borrowed a potential 5-year survival advantage of 25% for patients with occult disease from a retrospective study by Roses et al.[2] He concluded that the therapeutic benefit of routine ELND for such patients was not justified.

Two randomized, prospective trials have concluded that there is no advantage to ELND among patients with clinical Stage I disease.[3,4] Nevertheless, numerous retrospective studies have found a significant survival benefit for this procedure. Analysis of the study techniques reveals an explanation for the conflicting conclusions.

In prospective clinical trials patients may be seen every 1–2 months and told to return promptly if a node becomes palpable. Veronesi et al. reported a 50% 5-year survival among N_{1b} patients, who developed nodal disease during attentive follow-up.[3] Survival was equally good for N_{o+} patients who had occult metastases at elective dissection. These patients suffered only the staging consequences of their pathological Stage II disease.

Patients whose nodal disease is allowed to progress suffer the more serious tumor burden consequence of their clinical Stage II disease. Most retrospective studies focus attention on the many variables associated with the primary lesion. Changes in lymph nodes are seldom reported in a quantitative fashion. Investigators who report benefit from ELND should report the number and size of positive nodes recovered at delayed dissection. The excess deaths that occur among these patients are most likely the result of distant metastases seeded from relatively advanced regional disease. This thesis should be simple to verify. Silberman should be commended for carefully including this data in his paper. His advice to defer regional node dissection is sound. The calculated, potential benefit is small, and careful follow-up of intact regional nodes produces equally good results.

Melanoma appears to follow biologic principles previously suggested for breast cancer.[5] The thoughts expressed here are best understood in light of that hypothesis.

RICHARD A. EVANS, M.D.
Houston, Texas

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Dear Editor:

I would like to thank Dr. Evans for his kind comments. His hypothesis regarding the reason the retrospective studies have consistently demonstrated a survival advantage while the prospective studies have not may well be correct.

I would like to point out, however, that although it does not appear that prophylactic regional lymph node dissection (PRLND) offers a significant therapeutic benefit, I often perform the procedure for prognostic and staging information. The problem with which one is faced is that the patient whose microstaging is sufficiently worrisome to make him/her a candidate for PRLND is also the patient who should be considered for placement on an adjuvant trial. Most Stage I and II adjuvant trials require the lymph node dissection as an entrance requirement. Thus, the node dissection in melanoma becomes analagous to the axillary dissection for breast cancer, namely, the result of the dissection leads to a decision regarding systemic therapy. The point that must be made is that the patient must be made aware of the distinction between a therapeutic operation and a staging operation.

A. W. SILBERMAN, M.D.
Los Angeles, California

August 14, 1987

Dear Editor:

The paper entitled *Drug-induced esophageal strictures* by Bonavina et al. was most interesting.[1]

It is probable that esophageal ulceration and sometimes stricture is more common after drug ingestion than we know. After all, it is likely that reported cases are merely the tip of a very large iceberg. For the same reasons, the drug list in Table 2 is probably incomplete. A couple of years ago I was able to report a case of severe ulceration of the esophagus due to slow-release theophylline,[2] a commonly used drug. At that time only one other case had been reported.[3] In neither of these two cases did stricture result, but one could postulate that many strictures are treated in their late stages long after the initial insult has been forgotten. It is therefore worth repeating once again Evans' advice that tablets should be taken either before or during meals and washed down liberally with adequate fluid.

JULIUS L. STOLLER, M.B., F.R.C.S.(E), F.R.C.S.(C), F.A.C.S.
Vancouver, Canada

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October 8, 1987

Dear Editor:

I appreciate Dr. Stoller's addition of the drug theophylline to the list of drugs known to have caused esophageal injury. I apologize that our search did not uncover his publication. I wish to underscore his statement that "it is likely that the reported cases are merely the tip of a very large iceberg." No doubt there are many other drugs that could be added to the list. I concur with his quoting of Evans' advice that tablets should be taken either before or during meals and washed down liberally with adequate fluid. His advice certainly is sound. I wish he would have told us who Evans was.

TOM R. DEMEESTER, M.D.
Omaha, Nebraska

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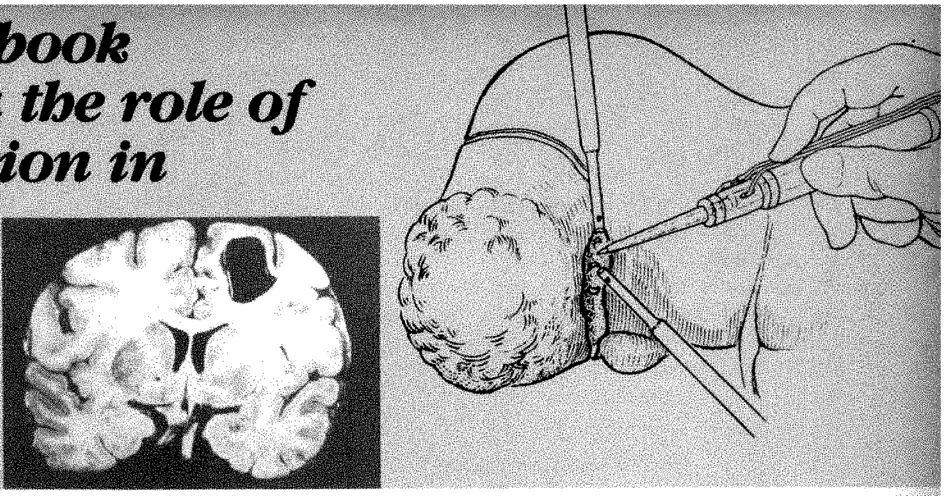

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Edited by Steven A. Rosenberg, M.D., Ph.D.

Chief of Surgery, National Cancer Institute, Bethesda, MD.

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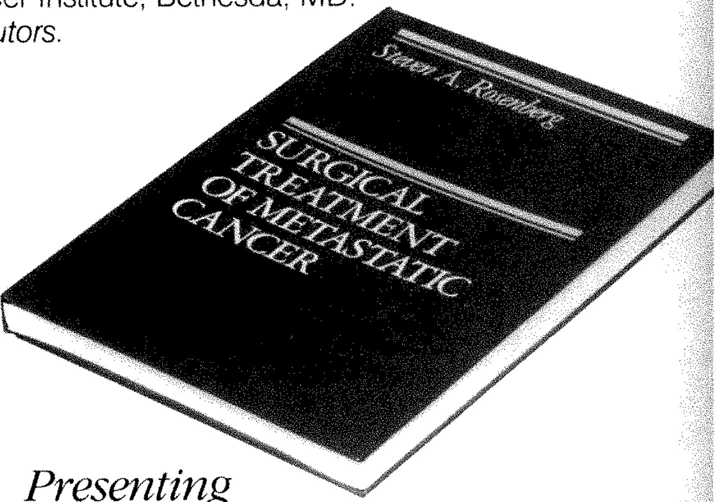

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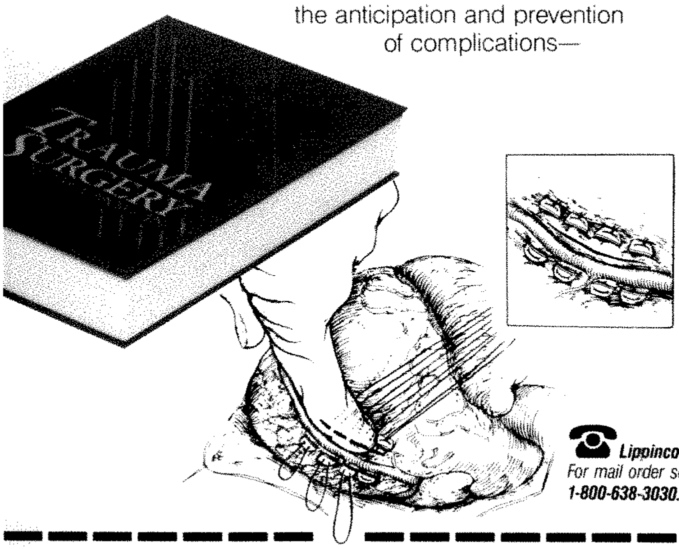

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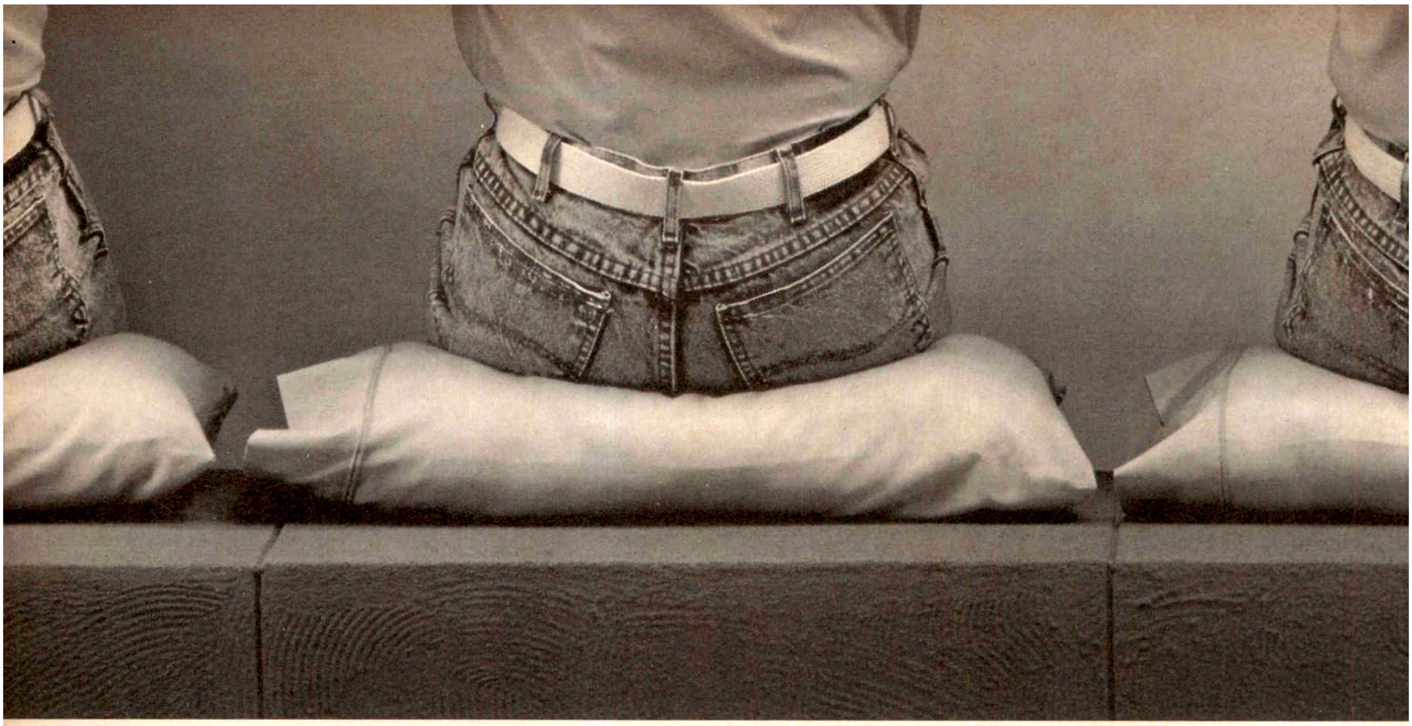

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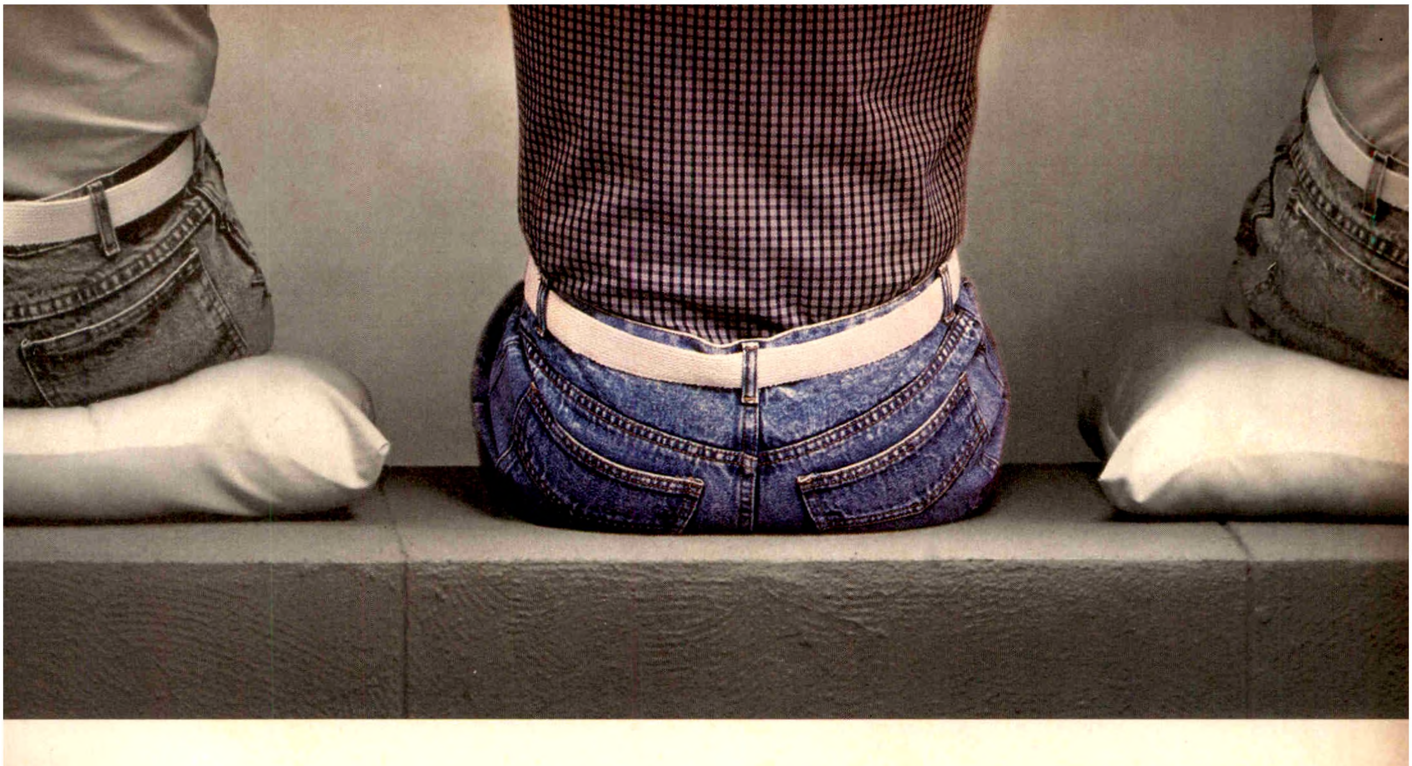

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INDICATIONS AND USAGE: Topical corticosteroids are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.
CONTRAINDICATIONS: Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.
PRECAUTIONS: ***General:*** Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia and glucosuria in some patients. Conditions which augment systemic absorption include the applications of the more potent steroids, use over large surface areas, prolonged use and the addition of occlusive dressings. Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area and under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids. Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See PRECAUTIONS—Pediatric Use.) If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted. In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.
Information for the Patient: Patients using topical corticosteroids should receive the following information and instructions: 1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes. 2. Patients should be advised not to use this medication for any disorder other than for which it has been prescribed. 3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician. 4. Patients should report any signs of local adverse reactions especially under occlusive dressing. 5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.
Laboratory Test: The following test may be helpful in evaluating the HPA axis suppression: ACTH stimulation test
Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids. Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.
Pregnancy Category C: Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women of teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.
Nursing Mothers: It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities NOT likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when any topical corticosteroids are administered to a nursing woman.
Pediatric Use: Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio. Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches and bilateral papilledema. Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.
ADVERSE REACTIONS: The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximately decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, miliaria.
OVERDOSAGE: Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects. (See PRECAUTIONS.)
DOSAGE AND ADMINISTRATION: Topical corticosteroids are generally applied to the affected area as a thin film three or four times daily depending on the severity of the condition. Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions. If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted.
HOW SUPPLIED: 1 oz. tube with rectal applicator.
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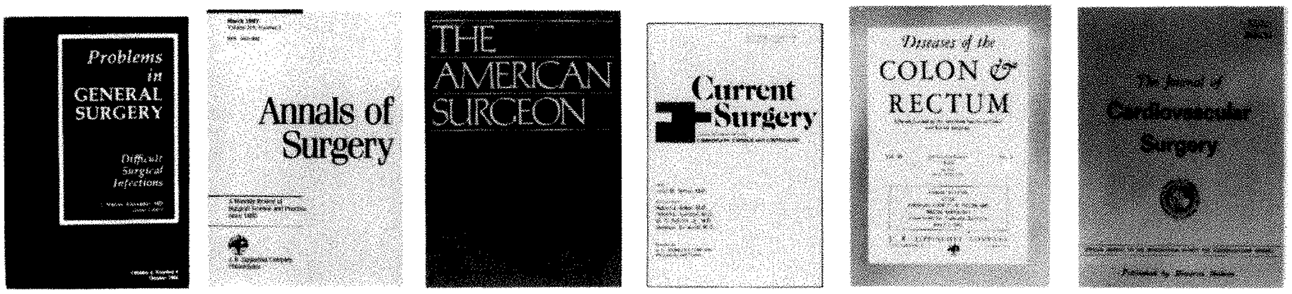

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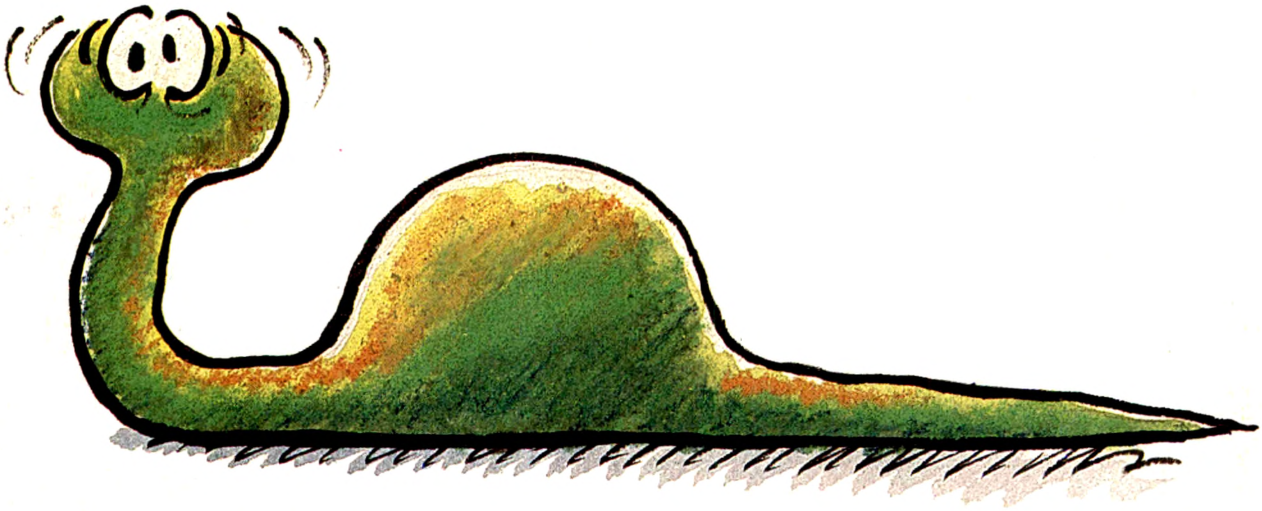

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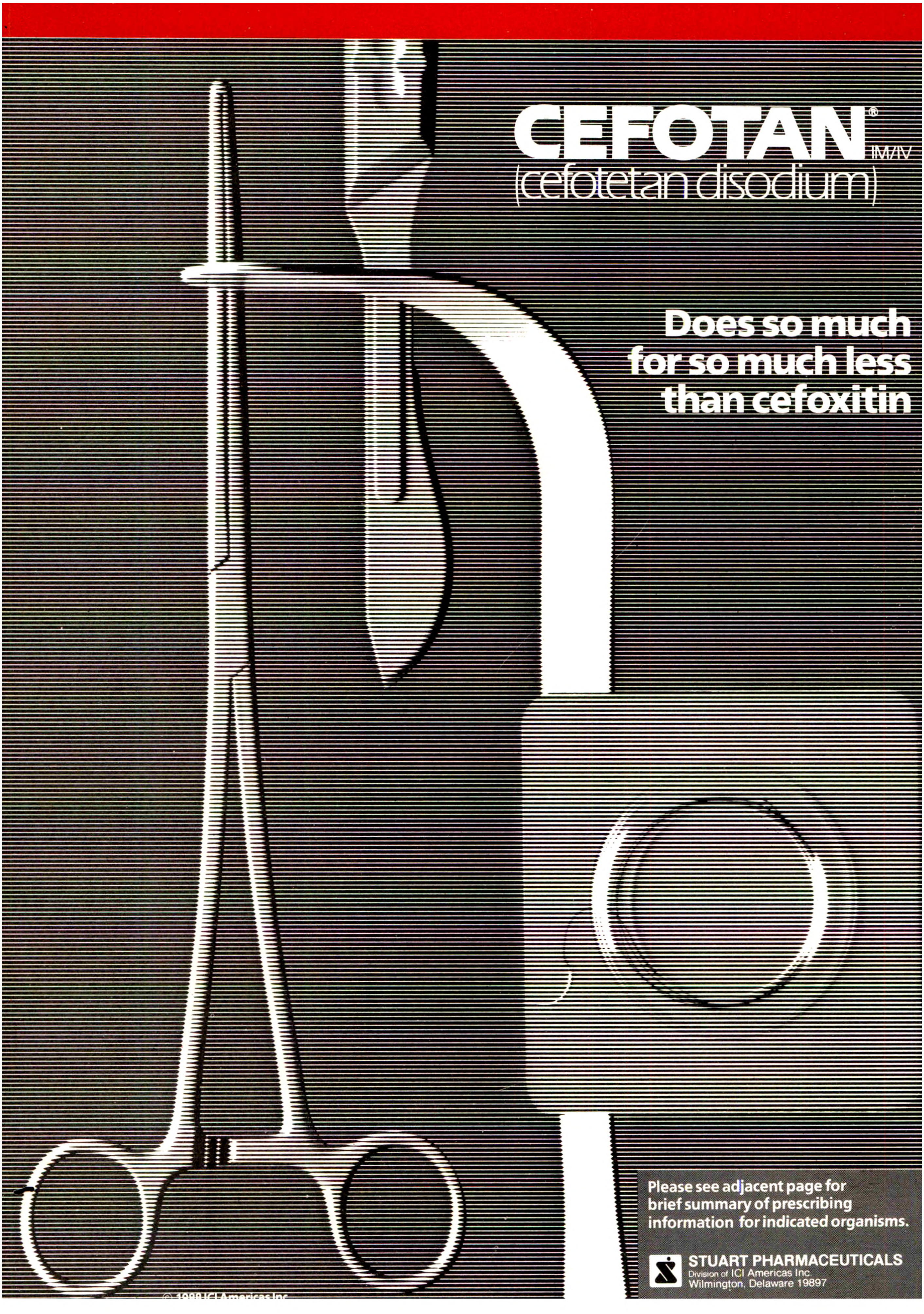

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BRIEF SUMMARY

INDICATIONS AND USAGE

TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary tract infections caused by *E coli, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris, Providencia rettgeri*, and *Morganella morganii*).

Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli.*

Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis,* Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli.*

Gynecologic infections caused by *Staphylococcus aureus*† (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis,* Streptococcus* species (excluding enterococci), *E coli, Proteus mirabilis, Neisseria gonorrhoeae, Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*), *Fusobacterium* species,† and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species†).

Intra-abdominal infections caused by *E coli, Klebsiella* species (including *K pneumoniae*†), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*).

Bone and joint infections caused by *Staphylococcus aureus.*†

***NOTE:** Some strains of *Staphylococcus epidermidis* are resistant to cefotetan.

† Efficacy for this organism in this organ system was studied in fewer than ten infections.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile.* Other causes should also be considered.

PRECAUTIONS

GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state. Prothrombin times should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels of Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approx 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approx 2-4 times the usual human dose), only 1 of 10 treated animals was affected, and the degree of degeneration was mild. Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

CEFOTAN® (cefotetan disodium)

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In clinical studies the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5 percent of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4 percent of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2 percent of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2 percent of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than one percent of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

DOSAGE AND ADMINISTRATION

TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dose*	Every 12 hours
10-30	Usual Recommended Dose*	Every 24 hours
<10	Usual Recommended Dose*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED

CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

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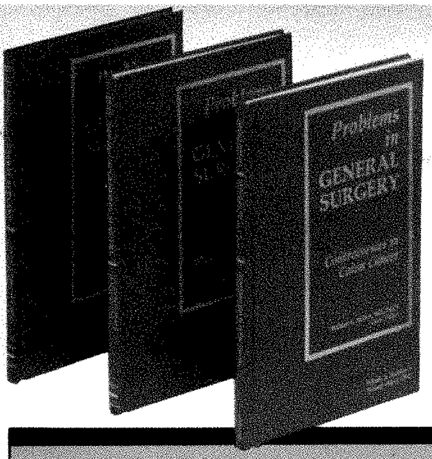

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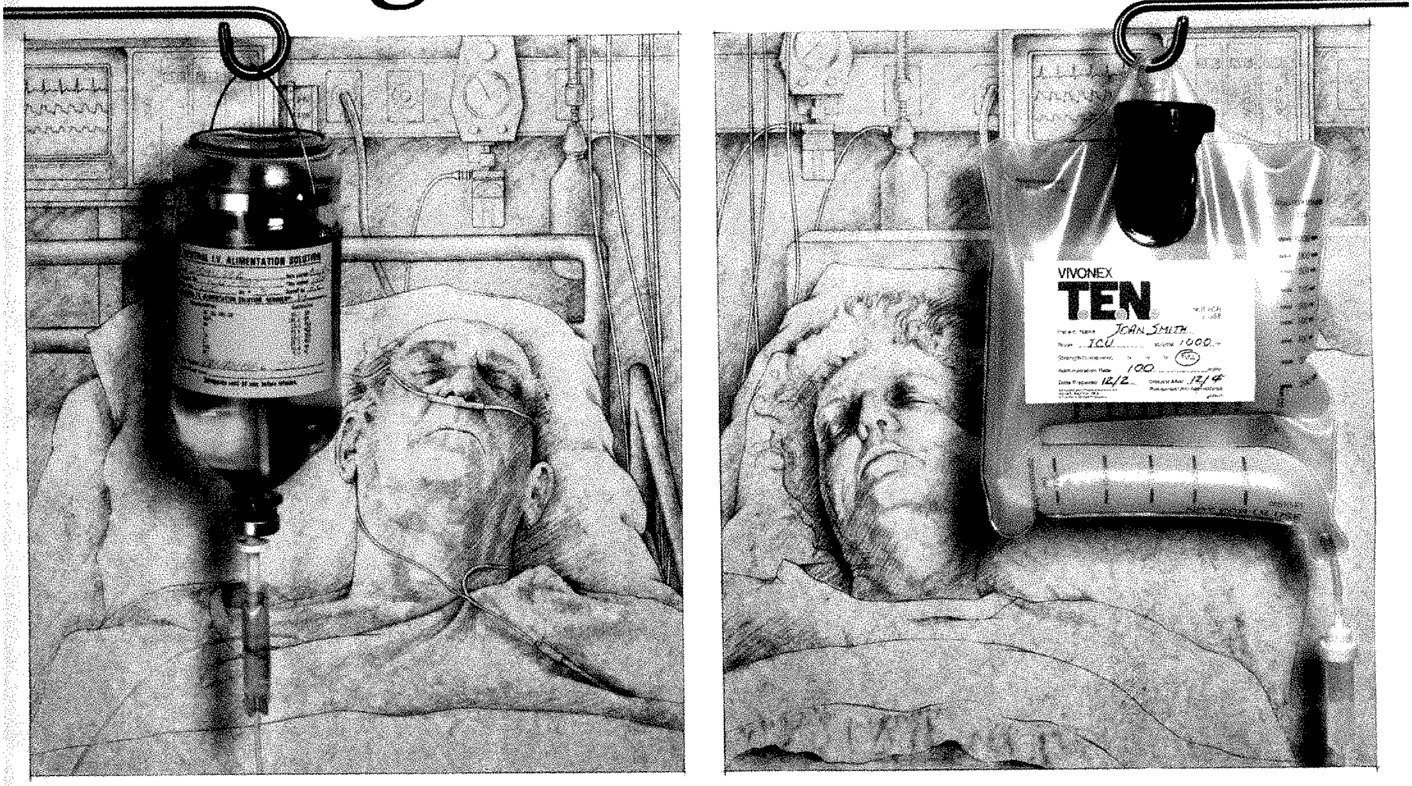

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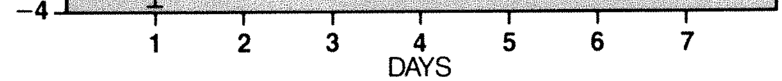

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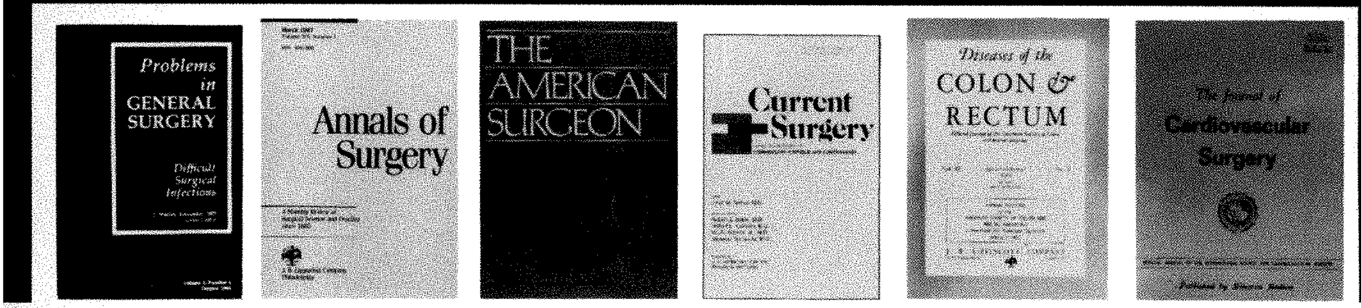
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WARNING: Because of its action in the clotting mechanism, Thrombostat must not be injected or otherwise allowed to enter large blood vessels. Extensive intravascular clotting and even death may result. Thrombostat is an antigenic substance and has caused sensitivity and allergic reactions when injected into animals.

PRECAUTIONS: General: Consult the absorbable gelatin sponge product labeling for complete information for use prior to utilizing the thrombin-saturated-sponge procedure.

Pregnancy—Teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with Thrombin, Topical (Bovine). It is also not known whether Thrombin, Topical (Bovine) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Thrombin, Topical (Bovine) should be given to a pregnant woman only if clearly indicated.

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DOSAGE AND ADMINISTRATION: General: Solutions of Thrombostat may be prepared in sterile distilled water or isotonic saline. The intended use determines the strength of the solution to prepare. For general use in plastic surgery, dental extractions, skin grafting, neurosurgery, etc, solutions containing approximately 100 units per ml are frequently used. For this, 10 ml of diluent added to the 1000 unit package is suitable. Where bleeding is profuse, as from cut surfaces of liver and spleen, concentrations as high as 1000 to 2000 units per ml may be required. For this the 5000 unit vial dissolved in 5 ml or 2.5 ml respectively, of the diluent supplied in the package is convenient. Intermediate strengths to suit the needs of the case may be prepared by selecting the proper strength package and dissolving the contents in an appropriate volume of diluent. In many situations, it may be advantageous to use Thrombostat (Thrombin, USP) in dry form on oozing surfaces.

Caution: Solutions should be used the day they are prepared. The solution may be used for up to 6 hours when stored at room temperature; up to 24 hours when stored under refrigeration, and, if necessary, up to 48 hours when stored frozen.

The following techniques are suggested for the topical application of Thrombostat.

1. The recipient surface should be sponged (not wiped) free of blood before Thrombostat is applied.
2. A spray may be used or the surface may be flooded using a sterile syringe and small gauge needle. The most effective hemostasis results when the Thrombostat mixes freely with the blood as soon as it reaches the surface.
3. In instances where Thrombostat in dry form is needed, the vial is opened by removing the metal ring by flipping up the plastic cap and tearing counterclockwise. The rubber-diaphragm cap may be easily removed and the dried Thrombostat is then broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.
4. Sponging of treated surfaces should be avoided in order that the clot remain securely in place.

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1. Prepare Thrombostat solution of the desired strength.
2. Immerse sponge strips of the desired size in the Thrombostat solution. Knead the sponge strips vigorously with moistened gloved fingers to remove trapped air, thereby facilitating saturation of the sponge.
3. Apply saturated sponge to bleeding area. Hold in place for 10 to 15 seconds with a pledget of cotton or a small gauze sponge.

Thrombostat Kit: Thrombostat Kit contains one sterile 20,000 unit vial of Thrombostat, one sterile vial of Isotonic Saline Diluent, and one sterile pump sprayer cap. The Kit may be used as follows:

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2. The cover to the sterile inner tray is removed by pulling up on the finger tab, exposing the sterile contents.
3. Thrombostat solution of the desired strength is prepared and the pump sprayer cap inserted and seated on the Thrombostat solution vial. Note: Several strokes of the pump sprayer will be required before the Thrombostat solution is expelled.
4. Alternatively, when Thrombostat in dry form is needed, the vial is opened as described above and the dried Thrombostat broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.

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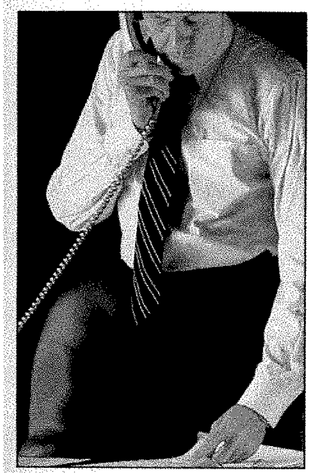

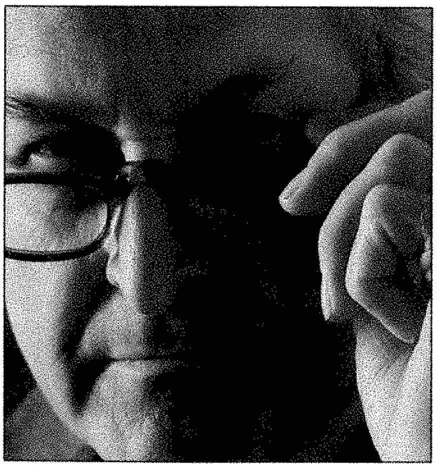

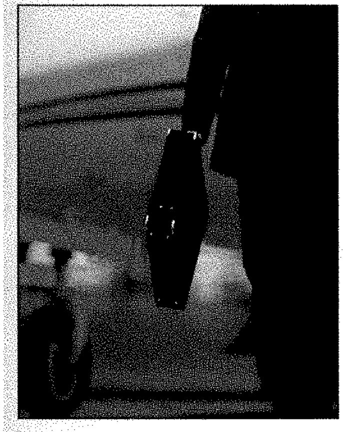

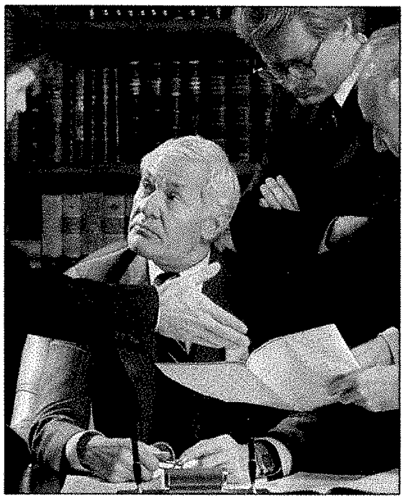

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[1] National Center for Health Statistics for 1985.

[2] A complete list of clinical evaluators is available upon request.

May 1988
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Annals of
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Presidential Address: The Origin and Early Development of the Southern Surgical Association

JOHN L. SAWYERS, M.D.*

From the Department of Surgery, Vanderbilt University School of Medicine, Nashville, Tennessee

As we celebrate the one hundredth birthday of this association, it is appropriate to reflect on the origin of the Southern Surgical Association, which was founded in 1887. What was happening in the United States at that time? Grover Cleveland was President of the United States in 1887, and we had no Vice-President. Cleveland was confronted with a revenue surplus and asked Congress for tariff reductions. How President Reagan would envy that situation!

Cleveland keynoted the centennial celebration of the Constitution. Of interest to the South, President Cleveland ordered the war booty of the Union Army, consisting of captured Confederate flags, to be returned.

Yale had defeated Harvard in football and was considered the national football championship team. Oklahoma did not have a football team and was not even a state until 1907.

Men's clothing fashions were knickers with straw or bowler hats. Audiences were thrilled by Buffalo Bill's Wild West Show featuring Annie Oakley. Edison invented the motor-driven phonograph that played cylinder records. Other inventions included the player piano, the gramophone, and the first electrocardiogram. Table 1 compares life in the United States in 1887 with 1987. The gasoline-engine automobile was not yet in the United States—Daimler ran his first car in Germany in 1886. The first automobile in the U.S. was introduced in 1893 by Duryea. Airplanes were only a dream. Richard W. Sears, a former railroad clerk, and A. C. Roebuck, a watchmaker, developed an innovative form of mail order merchandising.

Discoveries and events occurring in 1887 in medicine are listed in Table 2.

At the time of these events, two brothers, W. E. B. Davis and J. D. S. Davis, founded this association in Birmingham, Alabama. Dr. W. E. B. Davis recalls the origin of "the Southern" in his Presidential Address given in 1902 at the fifteenth session of the Southern Surgical and Gynecological Association.[1] W. E. B. Davis and his brother were editors of the *Alabama Medical and Surgical Journal*. This journal was their first joint

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* Professor and Chairman.

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TABLE 1. *U.S.A. 1887–1987*

	1887	1987
Population	59,217,000	239,743,000
Three-bedroom home	$2,100	$78,843
Average income	$431	$29,212
Eggs, 1 dozen	$0.19	$0.86
Bread, 1 pound	$0.05	$0.63
Milk, 1 gallon	$0.25	$2.22

venture. The journal was not successful, and publication stopped after 11 months. However, this journal stimulated the Davis brothers to propose a new medical society to be named the Alabama Surgical and Gynecological Association. The organizing meeting was held in November 1886 in the office of the *Alabama Medical and Surgical Journal.* The Davis brothers, conferring with a few prominent physicians from Birmingham, set December 15, 1886 as the organizational meeting date. Invitations were extended to fifty of Alabama's prominent physicians. The response was good.

Dr. H. N. Rosser of Birmingham was elected President and W. E. B. Davis was elected Secretary. In addition to Alabama physicians, 12 leading surgeons in the South were elected to honorary membership. Davis suggested this so that these prominent surgeons could serve as a nucleus to form a Southern association at a later date. Only one regular meeting was ever held—on October 11–12, 1887.

The Davis brothers, in their journal, had led an editorial attack regarding medical licensure in Alabama. The Davises proposed a single state medical licensing board; however, Dr. Jerome Cochran, who had organized the Alabama State Medical Association, favored a licensure of medical examiners in each county. Furthermore, the Davis brothers urged that only medical school graduates be eligible for licensure examination. Dr. Cochran was the most politically powerful figure in Alabama medicine. He opposed the proposed Alabama Surgical and Gynecological Association on the grounds that this new society might weaken the Alabama Medical Association. Dr. W. E. B. Davis went to Europe for 6 months in early 1887. His brother could not carry on alone the fight with Dr. Cochran.

TABLE 2. *Discoveries and Events Related to Medicine—1887*

Bruce discovers cause of Malta fever.
Fell introduces intratracheal anesthesia.
Reed does first suture of pericardium.
Sir William Gowers and Sir Victor Horsley operate on the spinal cord (1st time).
Phenacetin discovered as an analgesic.
American Orthopedic Association founded.
Sloan Maternity Hospital opened in New York City.
Gram introduces diuretin.

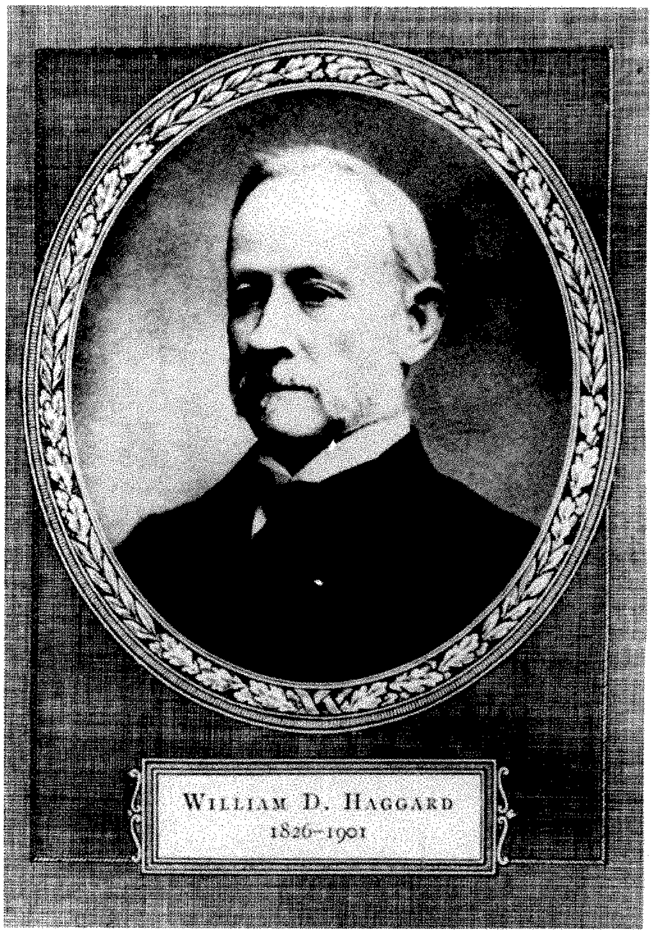

FIG. 1. W. D. Haggard—first president of the Southern Surgical and Gynecological Association, 1887–1888.

In March 1887, the Alabama Medical Society voted to continue the county examining licensure boards. The *Alabama Medical and Surgical Journal* was never published after May 1887. When W. E. B. Davis returned from Europe, he realized that the Alabama Surgical and Gynecological Association was in jeopardy with Cochran's opposition. Alternatives were discussed with the distinguished honorary members from outside Alabama. The decision was made to invite surgeons throughout the South to attend the October 1887 meeting with the idea of forming—instead of the Alabama Surgical and Gynecological Association—a new society to be named the Southern Surgical and Gynecological Association. Eighty replies were received in support of this idea. The Alabama Surgical and Gynecological Association met on October 11, 1887. On the second day of the meeting, October 12, 1887, the idea of forming the Southern Association was brought forth. Present was Dr. W. D. Haggard of Nashville, who argued eloquently in favor of a Southern organization (Fig. 1). The membership agreed. The Southern Surgical and Gynecologi-

TABLE 3. *Officers of the Southern Surgical and Gynecological Association—1887*

W. D. Haggard—President
W. E. B. Davis—Secretary
J. S. Cain—Chairman, Judicial Council
J. D. S. Davis—Chairman, Arrangements

cal Association was formed, with W. D. Haggard as President and W. E. B. Davis as Secretary. Dr. J. S. Cain of Nashville was elected chairman of the Judicial Council and J. D. S. Davis as chairman of the Committee on Arrangements (Table 3). As W. E. B. Davis writes: "The ablest men in the South, although absent, were elected to fill the other places on the Council." All promptly wired in their acceptance. Birmingham was selected as the next meeting place. The second Tuesday of November was the agreed-upon date; however, due to yellow fever, the meeting was delayed to December 4–6, 1888. By the time of this meeting, 90 members had been enrolled. The Southern Surgical Association was born.

The Davis Brothers

Who were these Davis brothers who at such a young age (24 and 28 years old) managed to organize this distinguished surgical organization?

William Elias Brownlee Davis

William Elias Brownlee Davis (Fig. 2) was born on November 25, 1863 in Trussville, Alabama. His father, Dr. Elias Davis, joined the Confederate Army and was killed while commanding sharpshooters at Petersburg, Virginia, before William Davis' birth.[2] William Davis represented either the third or fifth generation of physicians in the family. Carmichael[2] writes "third generation," whereas Moore's[1] article states "fifth." Davis' grandfather, Dr. Daniel Elias Davis, was an early settler of Alabama. William Davis had a brother, John D. S. Davis, who was 4 years older. Their widowed mother was a strong woman who, without the assistance of a husband, overcame the devastation caused by the war and raised her sons on a farm in Jefferson County, near Trussville, Alabama.

William Davis was educated in the schools at Trussville. He was considered the best student in Trussville High School. His grade average was 99.5%, the highest ever recorded in the school's history. He was able to enter directly into the junior class at the University of Alabama. Accomplishments at an early age marked his career. He decided to follow the family tradition of medicine. His medical education was unique even for those days, as he studied medicine at Vanderbilt University, the University of Louisville, and then Bellevue Hospital Medical College. His medical degree was obtained from Bellevue when he was 21 years old. He then returned to Alabama to join his older brother in practice.

FIG. 2. William Elias Brownlee Davis—founder of the Southern Surgical and Gynecological Association.

The Davis brothers worked together as a team in their endeavors. In 1894, William Davis and his brother—along with nine other men—established the Birmingham Medical College. William Davis assumed the position as Professor of Gynecology and Abdominal Surgery, only 10 years after graduating from medical school. He maintained this position until his death. John Davis was named Professor of Surgery.

That same year, 1894, the first hospital in Birmingham was started by the Davis brothers. This hospital was established to care for "women and surgical cases" and had a resident physician (Fig. 3).

Today, William Davis would be termed an "entrepreneur." He and John Davis founded a medical school that was the first in the country to provide an experimental surgery laboratory, a local hospital, a state medical journal, and organized the Southern Surgical Association. The Davis brothers collaborated on their experimental work, and credit was given to both for two notable investigations that were performed in the dog laboratory of the Birmingham Medical College. The Davis brothers reported their experience with 200 intestinal anastomoses performed in dogs. They demon-

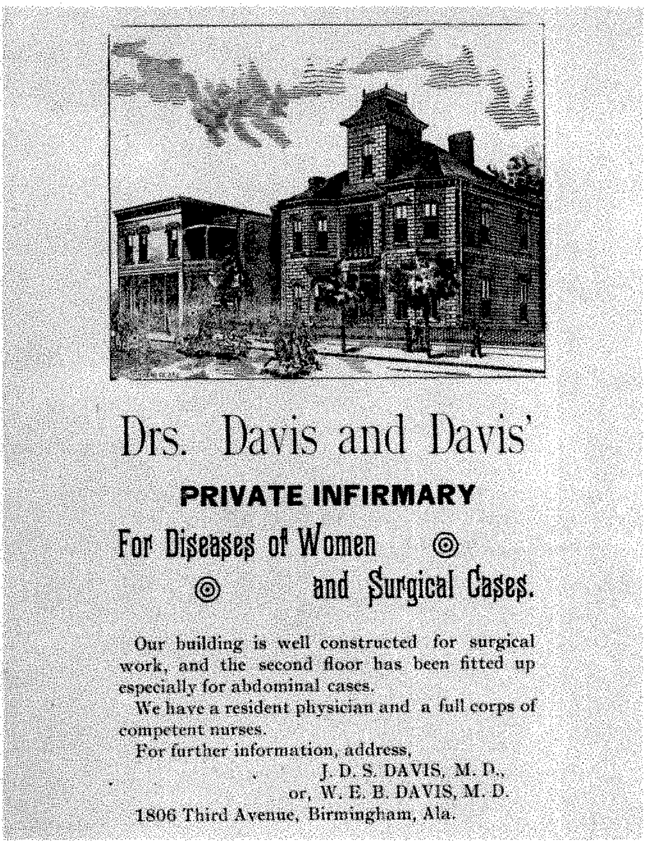

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FIG. 3. The Davis brothers established their private infirmary (hospital) in Birmingham in 1894.

strated that suture anastomosis was better than anastomosis by mechanical devices. Many debates ensued with surgeons who used the Murphy button. The second major accomplishment from their "dog lab" demonstrated the advantage of transperitoneal drainage of the common bile duct rather than suture closure after choledochotomy, which was standard practice at that time. Dr. W. J. Mayo praised the Davis brothers for this work.

TABLE 4. *Surgical Organizational Positions Held by W. E. B. Davis*

Year	Position
1886	Secretary, Alabama Surgical and Gynecological Association
1887–1900	Secretary, Southern Surgical and Gynecological Association
1901–1902	President, Southern Surgical and Gynecological Association
1889	Chairman, AMA Section for Obstetricians and Gynecologists
1890	Chairman, AMA Section on Surgery
1891	President, Tri-State Medical Society of Alabama, Georgia, and Tennessee
1892	President, American Association of Obstetricians and Gynecologists
1901	President, American Association of Obstetricians and Gynecologists
1902	Board of Censors, Medical Association of Alabama

TABLE 5. *Scientific Contributions of W. E. B. Davis**

Surgical treatment of biliary calculi
Operations for biliary duct obstruction
Intestinal anastomosis by suture vs. mechanical devices
Management of bullet wounds of the abdomen
Diagnostic value of peristaltic sounds
Technics of cholecystectomy
Treatment of gallstones
Postoperative care following celiotomy
Treatment of inflammation around the cecum
Charity hospitals
Control of water supply for Birmingham
Neurosis following oophorectomy
The medical profession's duty to the public
Philosophy regarding the role of a surgeon

* Modified from Carmichael.[2]

William Davis served as the first Secretary of the Southern Surgical and Gynecological Association and maintained this position for 14 years. In 1901, he was elected President. His talents were recognized by other organizations. He served as President of the Tri-State Medical Society of Alabama, Georgia, and Tennessee. Other offices held were chairman of the Section for Obstetrics and Diseases of Women for the American Medical Association and the next year, 1890, chairman of the Section on Surgery (AMA). He later was elected Vice-President of the American Medical Association. He was also President of the American Association of Obstetricians and Gynecologists in 1901 (Table 4).

Carmichael[2] lists his published scientific contributions, which included biliary surgery, intestinal anastomosis, management of bullet wounds of the abdomen, postoperative abdominal care, and treatment of inflammation of the colon (Table 5).

W. E. B. Davis was described as "fearless, saying always what he believes to be the truth. His motto was 'Defend the right, and denounce fraud whenever found.' " He believed in high standards and, as Secretary, ran "the Southern" in this manner. When the Southern Surgical and Gynecological Association was founded in 1887, Davis accepted the office as Secretary but was also made chairman of a committee empowered to select suitable members for the Association. All those who accepted membership and paid dues were enrolled as Founder members. Davis believed that there were few men in the South of great reputation compared to those from cities in the North and East. Therefore, Davis invited "men of great eminence from the entire country to join the Association." This made "the Southern" a national organization from its beginning. Today, about one fourth of the membership resides outside the South. However, Davis had to admit as Founding Members all the members of the Alabama Association who desired to join "the Southern." To quote him: "This necessarily admitted some members who should not have been received into the enlarged organization. It took several years to overcome this unfortunate complication." Davis solved this dilemma by not publishing the names of these "undeservable members" in the *Transactions* when they resigned or died. In his Presidential Address, Davis wrote "It would have been peculiarly unfortunate to have had the sketch of the life of an unknown man in Alabama appear in the *Transactions,* which would have been read by many eminent surgeons who would have judged the Association by this example. However, by tact on the part of the Council and Secretary, these men have gradually disappeared from the roll, having been dropped as a rule for non-attendance or the non-payment of dues, there being a By-Law which provides that a member who fails to attend for three consecutive meetings shall be dropped from the roll and another that a member failing to pay his dues for one year shall be dropped." Thus did Davis ensure the high standards that have existed for one hundred years for membership in the Southern Surgical Association.

Three months after his Presidential Address to "the Southern," William E. B. Davis was killed at a railroad crossing in Birmingham. Coroner W. D. Paris investigated the death and reported:

> "The death of Dr. Davis was an accident, pure and simple.
> "When Dr. Davis approached the crossing the flagman waved his red flag and Dr. Davis stopped his horse upon nearing the track on which the Alabama Great Southern train was passing. As he came to a stop he turned the horse to the left, facing the east. There was a space left between the horse and the moving train, and while the train was passing Dr. Davis got out of his buggy and went to the horse's head, going between the horse and the train.
> "When he reached the head of the horse, he caught the bridle and at the same time his foot was caught in one of the rails of the track next to that upon which the train was moving. He gave his foot a sharp jerk to release it, and as the member was released he lost his balance and fell under the train.
> "I saw all of the witnesses who could be reached, and after a full and careful investigation my official decision is that Dr. Davis met his death by accident. Neither he nor the railroad company was responsible for the affair."

Dr. W. E. B. Davis is buried in Oak Hill Cemetery in Birmingham.

The Southern Surgical and Gynecological Association held a series of eulogies at their next meeting. The Council appropriated funds ($2,000) for a monument to Davis.

The Davis Statue

The Southern Surgical and Gynecological Association commissioned Giuseppe Moretti to cast in French bronze the statue of W. E. B. Davis. Moretti, who was born in Siena, Italy, lived in Budapest and had achieved fame for his bust of the Austrian emperor Franz Josef. In 1888, Moretti emigrated to the United States and moved to Pittsburgh where he made several sculptures for Highland Park. His third commission after arriving in Pittsburgh was a statue of Cornelius Vanderbilt, which graces the campus of Vanderbilt University in Nashville.

Moretti's most famous work is Vulcan. The city of St. Louis invited Birmingham to exhibit at their Louisiana Purchase Exhibition in 1904. The Commercial Club in Birmingham engaged Moretti to cast an iron statue of the mythical god of fire and forge, Vulcan, from Alabama iron. Vulcan is the largest cast iron statue in the world, measuring 55 feet from spear tip to toe. The statue won the grand prize of the exposition. Vulcan now resides on a pedestal atop Red Mountain in Birmingham. Moretti moved to Birmingham after his success with Vulcan. His first commission in Birmingham was the W. E. B. Davis statue.[3]

On Wednesday, December 14, 1904 at 11:00 A.M., the Davis statue was given to the City of Birmingham. The public was invited to the unveiling and thousands attended. The procession began at City Hall and included Birmingham city officials, the Cadet Corps of Howard College, Memoli's Band, a detachment of the Alabama National Guard, and members of the Southern. Reverend L. S. Handley opened the ceremony with a prayer. Dr. William D. Haggard of Nashville was master of ceremonies. Dr. Davis' two young daughters unveiled the nine foot high bronze statue, which Charles M. Rosser of Dallas presented to the city. The Honorable John C. Forney accepted the statue for the City of Birmingham and Dr. R. M. Cunningham, acting Governor, accepted for the State of Alabama.

In 1952, it was noted that Davis' statue was tilting, not unlike the Leaning Tower of Pisa. Under the chairmanship of Dr. Joseph M. Donald (SSA President, 1961) and James M. Mason (SSA President, 1930), a committee of the Jefferson County Medical Society arranged for the statue to be relocated near the Hillman Building at the University of Alabama Medical Center. On November 4, 1957, the rededication ceremonies were held with Dr. George Finney, Secretary, and Dr. Floyd McRae, President of the Southern Surgical Association, making remarks. Dr. Robert C. Berson, Vice President, University of Alabama Medical Center and Dean of the Medical College, accepted the statue and promised that no tilting would be allowed on the medical college grounds. The statue was again unveiled by Davis' two daughters, Mrs. Elizabeth Batchelder of Warrenton, VA, and Mrs. Margaret Davis of Birmingham.

The statue bears this inscription at its base: "He would have been known to the world as a patriot had he not been known as something greater—a physician."

Gertrude Davis

William Davis' wife, Gertrude Mastin Davis (Fig. 4), was as interested in "the Southern" as her husband. She

FIG. 4. Gertrude Mastin Davis—W. E. B. Davis' wife and Honorary Fellow of the Southern Surgical Association.

attended most meetings and helped edit the *Transactions*. Gertrude Davis attended meetings of the Association after her husband's untimely death, and in 1931 was elected an Honorary Fellow of the Southern Surgical Association. She attended meetings until 1950 and died in 1953. During the first 100 years of "the Southern," she was the only woman to be elected to membership.

John Daniel Sinkler Davis

The older Davis brother, John Daniel Sinkler Davis (Fig. 5), was less outgoing than William. He was born in Trussville, Alabama on January 19, 1859 and was educated in the local schools. He graduated from the Medical College of Georgia in 1879. For two years he practiced general medicine in Ferryville, Alabama and then set up his office in Birmingham. He made friends with the coroner and undertaker, which enabled him to perform a large number of autopsies and to secure cadavers for dissecting purposes. This prepared him for the successful experimental surgical work that he and William did in later years. Of the two brothers, John was the one who pioneered in experimental surgery. One of his studies concerned gunshot wounds of the heart in dogs. He utilized cardiac massage and wrote that animals "apparently dead for an hour could be resuscitated by massage or kneading the heart between finger and thumb."[4] In 1893 he advocated early operation for head injuries with depressed skull fractures. He utilized plaster of Paris for fractures and performed open reduction of long bone fractures using silver bone plates.

J. D. S. Davis was more reserved than his younger brother but was described by his peers as a "great student, untiring original investigator in establishing fundamental surgical principles, teacher, organizer, leader and surgeon—a man of rare charm, culture and skill."[5]

When the Davis brothers established the Birmingham Medical College (Fig. 6), John D. S. Davis was appointed Professor of Surgery. When this institution was merged into the University of Alabama, he became Professor of Surgery at that medical school.

Truly Yours, J. D. S. Davis

FIG. 5. John Daniel Sinkler Davis—co-founder of the Southern Surgical and Gynecological Association.

John Davis never held an office in "the Southern," but he was made an Honorary Fellow when the Association changed its name in 1916 to the Southern Surgical Association, dropping the words "and Gynecological."

Like his brother, John D. S. Davis died as a result of an accident. He was involved in an automobile accident and died of complications from his injuries in 1931.

The 1888 Meeting

At the organization meeting of 1887, it was decided that the next meeting would be held in Birmingham. Dr. William David Haggard had been elected President of the newly formed Southern Surgical and Gynecological Association. Dr. Haggard was Professor of Gynecology and Diseases of Children, Medical Department, the University of Tennessee, then located in Nashville. The Chair held by Dr. Haggard had been established by Dr. Paul F. Eve and W. K. Bowling. He called the first annual meeting to order at the civilized hour of 10 A.M. on December 4, 1888, in the hall of the Young Men's Christian Association. Forty-one of the 90 members were in attendance, with 50 visitors.

The meeting was opened by an eloquent prayer by the Reverend Dr. D. I. Purser of Birmingham (Fig. 7). This custom of opening the meeting with a prayer was reinstated today by Dr. Raymond Ramage.

The Reverend Dr. Purser had an unusual background. He was born in Copiah County, Mississippi, December 24, 1843. He was raised on a farm. At the age of 17 years he joined the Confederate Army and served with an artillery company in 16 engagements. After the war, he entered business and rapidly made enough money to become financially independent. In 1870, he entered the ministry but never accepted a salary. In 1884, he accepted the call from the First Church, the only white Baptist Church in Birmingham. The membership increased from 278 to 500. Not only did he develop his own church but established four other Baptist churches, often using his own funds.

His first wife died in 1879. He married Sallie Moody of Tuscaloosa in 1883. She was the daughter of Judge Washington Moody, a man of great wealth and influence. Her brother, Frank Moody, was President of the First National Bank in Tuscaloosa. An energetic woman, she taught Sunday School and helped advance her husband's ministry.

Dr. Purser was described as a sensational, evangelical preacher. To this comment he replied "Sensation is better than stagnation."[6]

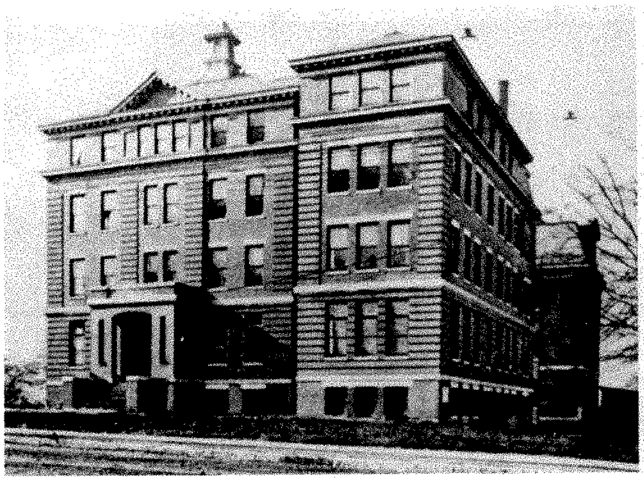

FIG. 6. The Birmingham Medical College, established by the Davis brothers in 1894, was merged into the University of Alabama Medical Center. The building as it appeared in 1903.

The Honorable A. O. Lane (Fig. 8), mayor of Birmingham, delivered a welcoming address, which is published in Volume I of the *Transactions*. Secretary Davis is reported to have remarked "It was the most beautiful welcoming address that I have ever listened to in my life."[7]

The Secretary then read a synopsis of the published minutes of the meeting for a permanent organization. A

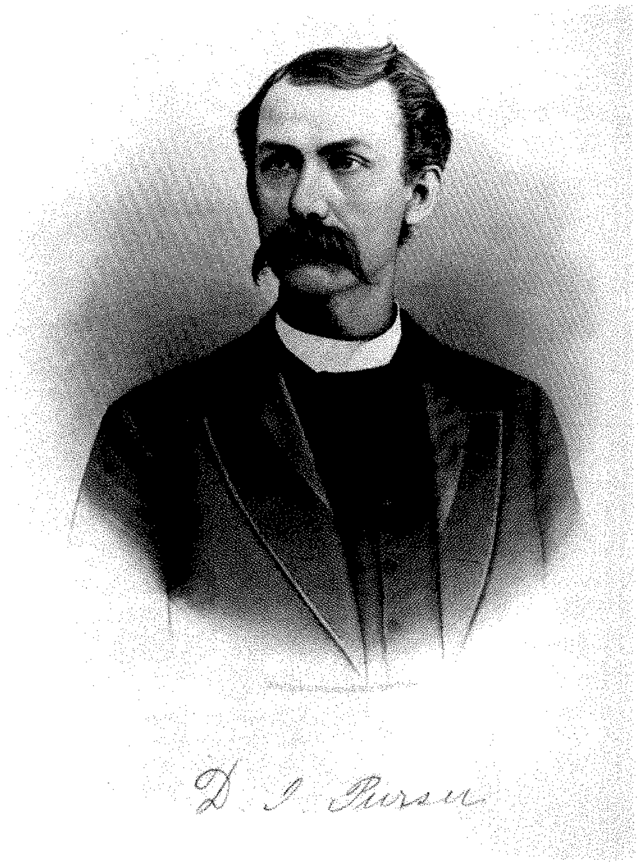

FIG. 7. Reverend Dr. D. I. Purser, whose eloquent prayer opened the first scientific session of the Southern Surgical and Gynecological Association in Birmingham, 1888.

FIG. 8. A. O. Lane, mayor of Birmingham, who delivered the welcoming address at the first scientific session of the Southern Surgical and Gynecological Association in Birmingham, 1888.

report was given by Dr. J. D. S. Davis, chairman of the Committee on Arrangements. Dr. Haggard appointed four members to serve on the Judicial Council with Dr. J. M. Taylor of Mississippi (the only member of the Council present). A motion was made to limit the membership in the Association to one hundred. This was referred to the Judicial Council, which reported back the next day that in its opinion it would not be wise to limit the membership to any specific number, and that the intent of the resolution could be attained in another and better way, by recommending that the standard of requirements for membership be fixed so high that only the best men would be eligible.

Dr. Haggard's Presidential Address praised J. Marion Sims for his contributions to gynecology and credited Ephraim McDowell for the founding of abdominal surgery. Haggard states that "The outcome of the labors of these two remarkable men in beneficient results has no parallel in the annals of medicine. They conferred on America the honor of being the birthplace of Gynecology, and did more to alleviate the sufferings, restore the health and prolong the lives of women than any two men living or dead." He then eloquently stated the need for the Association and welcomed into membership those "men as have by their works entitled them to the distinction of being educated, talented and industrious workers in the field of scientific research." His concluding remarks pointed out the trend toward specialization, emphasizing the danger of surgeons becoming deficient in the fundamental principles of medicine as a whole but supporting the trend toward specialization as exemplified by Sims' achievements.

The first scientific paper on the program was given by W. B. Rogers from Memphis, Tennessee. Entitled "On the Operation of Gastrostomy, With a Report of a Successful Case," Rogers presented a patient with a lye stricture of the esophagus. He had brought the patient with him and demonstrated the gastrostomy through which food was introduced through a silver tube. A mortality rate of 29.47% for gastrostomy performed for cicatrical stricture of the esophagus had been reported by Samuel W. Gross. The surgeons present were greatly interested in Rogers' successful result. He wrote that gastrostomy was indicated to prevent starvation but warned against using gastrostomy for patients with malignancy, stating "life can, at best, only hope to be prolonged for a very brief space—the wolf only driven from the door, while the jackal within devours the household."

Eighteen scientific papers were presented in addition to the Presidential Address. Eleven other papers were read by title. All papers were published in the *Transactions,* Volume I. Perhaps the most interesting paper was given by John R. Page, former Professor at the University of Virginia, entitled "Shock of Injury." This paper would probably have won the Shipley award, if an award had been given. Page described four young men seriously injured in railroad accidents. All survived despite a loss of consciousness and evident shock. One patient fell 52 feet from a train trestle, the second and third patients fell with their engine through a trestle 25 feet into a creek bed; five coal cars tumbled in on the engine. The fourth man was severely mashed between two railroad cars while attempting to couple them. After transporting the patients to a nearby hospital, Page performed suture of lacerations and cleansing of contusions and abrasions, but no other operation. He avoided bloodletting and sedation early after injury. General supportive care, bed rest, evacuation of the urinary bladder by catheter, morphine for pain, and nutritive enemas resulted in recovery of all four patients.

In the evening the members attended the opera house for musical entertainment and an annual oration by W. F. Hyer, ex-President of the Mississippi State Medical Association. Hyer spoke about the relationship that exists between the physician and his patient. This speech is published as the last article in Volume I of the *Transactions.* On the last day of the meeting the rules of the

Association were temporarily suspended, whereupon Dr. Rogers moved that Article XV of the By-Laws providing for an annual oration be stricken out. The motion passed without dissent. Perhaps it was the late hour. At any rate, Dr. Hyer's oration was the first and the last presented to the Southern Surgical Association.

At this meeting, Hunter McGuire of Richmond was elected President. Dr. McGuire was not present but wired his acceptance. Hunter Holmes McGuire's presidency ensured the success of the Association. He was a nationally recognized leader. He served as President of the American Surgical Association in 1886 and President of the American Medical Association in 1893. As John W. Long wrote in his Presidential Address in 1914, "No organization could fail to go when inspired by the enthusiasm of Davis, censored by the wisdom of Haggard, and vitalized by the magic touch of McGuire."[8] This trio was like the Ninth Wave. Our ancestors who lived near the ocean believed that there is always one wave that comes along that is larger than any preceding wave. This was called the Ninth Wave. This results from a remarkable combination of wind and sea. Special skill and time are needed to catch the Ninth Wave at its crest. Davis, Haggard, and McGuire—like the Ninth Wave—instituted significant change in surgery in the South. Their timing was perfect. The Southern Surgical Association rode the wave to the top during this past century.

Will the next hundred years be as fruitful? Arlie Mansberger, in his Presidential Address last year, illuminated some of the challenges that face us now: malpractice litigation, cost-restraining measures, DRGs, PROs, HMOs, PPOs, IPAs, physician reimbursement, turf battles, fragmentation, funding for graduate education and, indeed, medical education in general. Problems like these recall William French Smith's comments to incoming Attorney-General Edwin Meese. Smith remarked that some days Meese would feel like "the javelin competitor who won the toss of the coin and elected to receive."[9]

A glance backward at our history can only lead to optimism. The giants of Surgery have, are, and will be fellows of the Southern Surgical Association. Just as we have climbed forward on the shoulders of our past members, so shall we advance in the future. Hunter McGuire, in his Presidential Address, predicted that "this Society will become one of the most important in this country."[10] Indeed, it has. McGuire concluded his address with these words:

> "Gentlemen of the Southern Association, let our motto be lofty aim and united action. As Southern men, let us show to the world that, under changed conditions, we have still the stamina of our forefathers. As members of our beloved profession, let us strive to be first in scientific attainment, first in integrity, first in high purpose for the good of mankind."

I can conclude with no better words than those, so eloquently said in Nashville, Tennessee in 1889.

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Renaissance Man of the Southern Surgical Association

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THE SOUTHERN SURGICAL ASSOCIATION met in many different cities during the late 19th century. The sixth meeting, held in 1893, was the first to be held in New Orleans. During the welcoming speech, Dr. A. B. Miles, the local arrangements chairman, noted that one of the outstanding institutions in New Orleans was Charity Hospital. This institution, which had been in operation since 1736, was the major teaching hospital for the University of Louisiana, which soon became Tulane University. The demonstrator in anatomy at Charity Hospital at the time of this meeting was Dr. Rudolph Matas, who, the following year, became professor of surgery at Charity Hospital and was appointed the Chairman of the Department of Surgery at Tulane University, succeeding Dr. A. B. Miles. At this first meeting attended by Dr. Matas, he participated in the discussion of a paper by W. T. Briggs on the treatment of bladder stones. Interestingly, the minutes of the meeting do not reflect Dr. Matas's election to membership, but he is listed as a member elected in 1893 in the *Transactions of the Southern Surgical and Gynecological Association* for 1894 and in all volumes of the *Transactions* since that time.

Dr. Matas was a native of Louisiana, born in Bonnet Carre in September 1860, the son of Dr. and Mrs. Narciso H. Matas, originally of Barcelona. He had a peripatetic childhood, moving as his family moved from place to place. His father, a physician, was engaged in investment activities in addition to his profession. During his formative years, Rudolph Matas lived in Barcelona, Spain, Paris, France, New Orleans, Louisiana, Brownsville, Texas, and Matamoros, Mexico. His formal education, therefore, was for short periods in many schools, but his remarkable intellectual capacity, his inquisitive mind, and his indefatigable energy were apparent at a very young age. He grew up as a multilingual young man, speaking English, French, Spanish, and subsequently Italian. Of equal importance, he read widely in all areas of knowledge. Thus, when he was graduated from St. John's Collegiate Institute in Matamoros, Mexico, he received prize copies of Jessup's *Botany*, Ganot's *Physics*, and Milne Edward's *Natural History* for leading his class in those subjects.

He had decided to follow in his father's footsteps in the profession of medicine and entered medical school at the University of Louisiana in 1877. On the basis of competitive examinations, he received an appointment as a resident medical student at Charity Hospital.

Dr. Matas was a man of irrepressible energy and vitality. Within a few years following his graduation, he had developed a rapidly growing private practice that claimed much of his time. In addition, however, he devoted a major portion of each morning to Charity Hospital as a visiting physician, and he fulfilled his editorial duties of the New Orleans Medical and Surgical Association. He organized a group that called itself the New Orleans Pathologic Society, composed of physicians trained and in training under Dr. H. D. Smith, a pathologist at Charity Hospital.

As is true of many such men, friends worried about his health. One friend stated that at the rate he was working he would plunge headlong toward a nervous or physical breakdown, and he was urged to decrease his activities. He, however, like some of his well-known successors, followed his own star and pursued goals which could not be denied.

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When one recognizes the fact that his reading was always done at the end of a busy day or very early in the morning before starting another busy day, his motivation and commitment to the acquisition of knowledge was remarkable.

Dr. Matas's insatiable desire for knowledge led to the accumulation of a large personal library that he kept in his home. When one of us (MED) was a medical student, the personal library of Dr. Rudolph Matas served as an extension of the library at Tulane University, particularly his subscriptions to foreign journals. By this time his entire home had become one large library, and the weight of the books was so heavy that the foundation of the house had to be reinforced to maintain this weight. Requesting to use some of his collection for study, he invited me to his house. This courtly gentleman invited me in, gave me a glass of wine and asked many questions concerning my activities, my family, and my long-term goals. As I was leaving with the books that I borrowed, he invited me to join him on his front porch on Mardi Gras. He lived on St. Charles Avenue and the parade passed in front of his house. When they reached this house, they stopped to drink a toast to Dr. Matas.

Dr. Matas was a prolific writer. He was graduated from medical school at the age of 20 years, and at the age of 23 years was selected as editor of the *New Orleans Medical and Surgical Journal.* While its editor, he regularly wrote editorials and was recognized as a writer who not only had a great deal to say, but presented his material in an engaging and interesting manner. In 1935, Dr. W. H. Anderson stated that, "The catalogue of his publications . . . on the most varied subjects, attest to his tireless industry, his amazing versatility and unsurpassed erudition." His publications number more than 500, the last which I could identify was in 1953 at the age of 93 years.

When the Southern Surgical Association met in 1893 in New Orleans, Dr. Matas was recognized as the outstanding physician in New Orleans. It had been anticipated that Tulane would conduct a search for a new Chairman of Surgery from outside of Louisiana, but a ground swell of local support by the citizens at large, as well as physicians, assured his appointment to this post. There were publications in the local press in his support and poetry written in his honor.

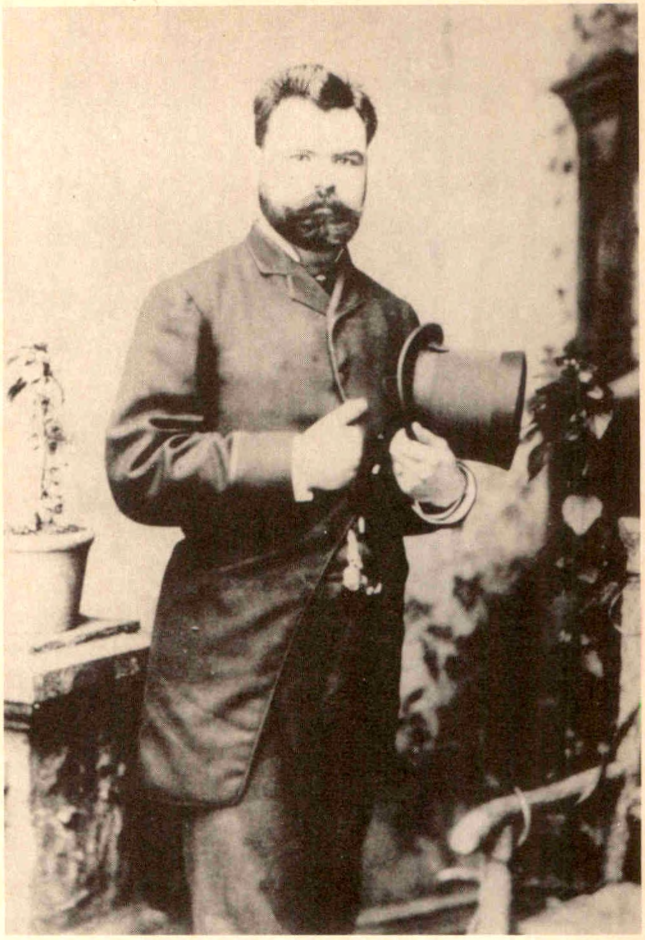

FIG. 1. A picture of Dr. Rudolph Matas circa 1884–85. (From Cohn I, Deutsch HB. Rudolph Matas. Garden City, NY: Doubleday and Co., 1960.

Under his leadership the Department of Surgery flourished. There were those who believed it impossible to begin a conversation on any subject about which Dr. Matas did not know more than those who introduced the conversation. One vignette involves an intern who had been searching for some obscure area of interest in which he might display his superior knowledge. He found such a subject in a Canadian medical journal and the next day engaged Dr. Matas in discussion. After listening to him, Dr. Matas commented that the subject he was discussing, and thoughts similar to those expressed by the intern, had been presented in a proprietory Canadian journal in its last issue, and referred the intern to this source if he wished to read further. Another student stated that if he attended Dr. Matas's lectures, operations, and rounds regularly, he did not need to read, because Dr. Matas would say all there was to say on all subjects.[1,2]

Dr. Matas served for 32 years as professor of surgery, stepping down as chairman of the department in 1927, when he was succeeded by Dr. Alton Ochsner. However, he continued to live in New Orleans until his death in 1957, just 3 years short of his one hundredth birthday. After retiring as chairman, he continued to operate, and performed his last operation on an 85-year-old patient in 1945 when he was 85 years old.

Dr. Matas attended the Southern Surgical Association on 22 occasions from 1893 to 1944, on the last occasion during his 84th year of life. He never attended without

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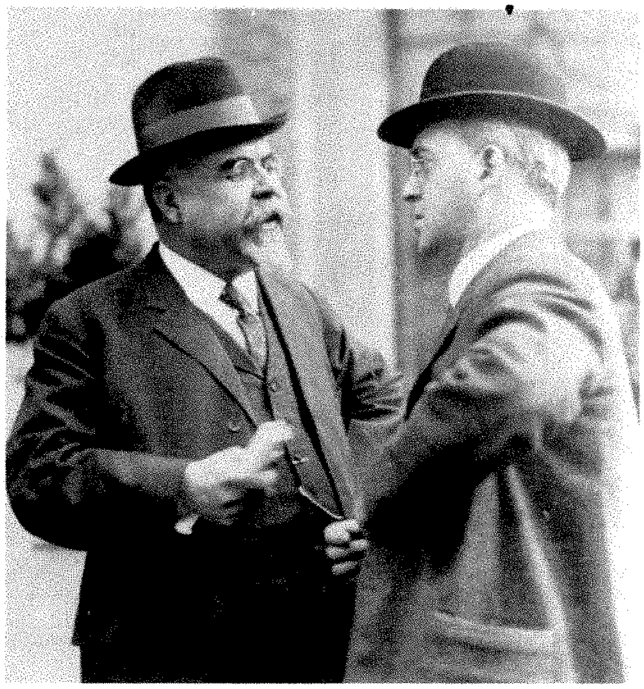

FIG. 2. Dr. Rudolph Matas in consultation with Dr. Hubert A. Royster. (From the private collection of Dr. Isidore Cohn, Sr., published with permission from Dr. Isidore Cohn, Jr.)

being an active participant. He presented 17 original papers and 29 discussions. At many meetings he discussed more than one paper. In fact, in 1932 he rose to discuss papers on five occasions. His discussions were always detailed, extensive expositions of the subject at hand. In fact, some of his published discussions are equivalent in length to an original paper. The breadth and depth of his knowledge was truly astounding.

Dr. Matas was probably best known for his contributions to vascular surgery, and eight of his original presentations were on vascular subjects. He was one of the first to recommend wiring and electrolysis for the treatment of abdominal aortic aneurysms and presented a paper on this subject at the Southern Surgical Association in 1900. A major contribution was the technique of endoaneurysmorrhaphy, which he first performed in the treatment of a traumatic aneurysm of the brachial artery in 1888. The treatment of the aneurysm by the usual method of ligature of the artery proximal to the aneurysm failed and shortly thereafter he ligated the vessel below the aneurysm and hoped to complete its cure. The aneurysm rapidly returned to its original size and force of pulsation. At the time of reoperation he controlled the circulation in the area by an Esmarch bandage. He opened the aneurysmal sac and observed large collateral vessels, which he closed by suture. The patient's wounds healed without complication and he was known to be alive and performing hard manual labor many years later. Dr. Matas did not repeat this operation until 12 years later and it was first reported before the American Surgical Association in 1902. His first discussion of this subject at the Southern Surgical Association was in 1911 when he discussed a presentation by W. C. G. Kirschner entitled, "The Matas Operation in the Treatment of Traumatic Aneurysm." His extensive experience with endoaneurysmorrhaphy was presented at the Southern Surgical Association in 1919 when he presented "Endoaneurysmorrhaphy. I. Statistics of Operation of Endoaneurysmorrhaphy. II. Personal Experiences and Observations on the Treatment of Arteriovenous Aneurysms by the Intrasaccular Method of Suture with

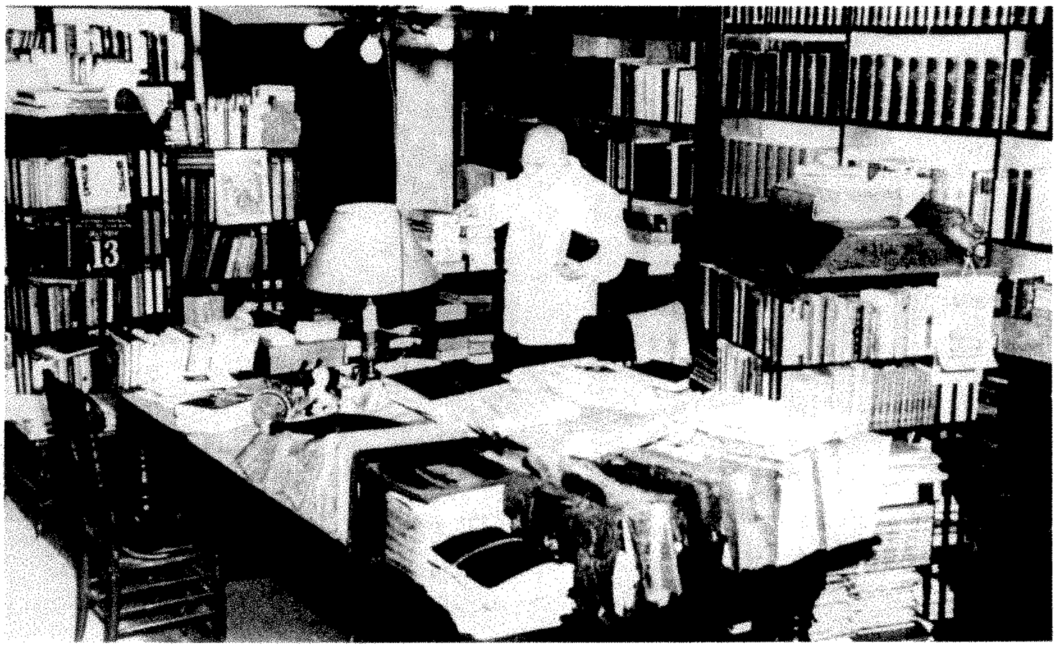

FIG. 3. Dr. Matas at home. Most of the rooms of his house were filled with books as shown here. (From Cohn I, Deutsch HB. Rudolph Matas. Garden City, NY: Doubleday and Co., 1960.

Special Reference to the Transvenous Route." By this time he was recognized as the premier vascular surgeon in the United States and subsequently he discussed papers on aneurysmal surgery on many occasions.[3]

Other vascular subjects on which he presented original papers include the systemic and cardiovascular effects of arteriovenous fistulas, a summary of his personal experience in the surgery of the subclavian artery, aneurysms of the Circle of Willis, and congenital arteriovenous angioma of the arm. He also discussed papers on lymphatic edema, mesenteric thrombosis, aneurysms of the temporal artery and later, aneurysms in the cervical portion of the internal carotid artery. At the last meeting he attended, at age 84, he discussed a paper by A. H. Blakemore and J. W. Lord, Jr., entitled, "A Nonsuture Method of Blood Vessel Anastomosis."

Although vascular surgery was the subject of many of his comments at the Southern Surgical Association, he presented papers on biliary tract disease, extra-uterine pregnancy, hair balls of the stomach, and trigeminal neuralgia, and discussed a variety of other subjects, including appendicitis, cystectomy for carcinoma of the bladder, hypodermoclysis, injection of the Gasserian ganglion for neuralgia, pseudomyxoma peritonei, ptosis of the spleen, scalenus anticus syndrome, and spinal and avertin anesthesia.[4-20]

In 1899, Dr. Matas presented a paper on the history and methods of intralaryngeal insufflation for the relief of acute surgical pneumothorax, with a description of the latest devices for this purpose. He was one of the first to use endotracheal intubation and positive pressure respiration in operations on the thorax. In the early 1900s he became interested in the administration of fluid and electrolytes and is credited with the first use of intravenous fluids (Table 1).[6]

Dr. Matas was elected to the office of President of the Southern Surgical Association and served in this capacity in 1911. He presented another innovative idea whose time had come. His presidential address was entitled, "The Cinematograph as an Aid to Medical Education and Research." His lecture was illustrated by moving pictures of ultramicroscopic life in the blood and tissues, as well as of surgical operations, and he demonstrated graphically the value of motion pictures as an educational tool. This idea, of course, rapidly became popular and since that time pictures on celluloid film or videotape have become standard instructional tools in all areas where dynamic action photographs can depict the subject at hand.[10]

He was an active member of the Southern Surgical Association for 34 years and was elected to honorary membership in 1927. He continued to attend meetings of the Association and to participate in the scientific activities for an additional 17 years.

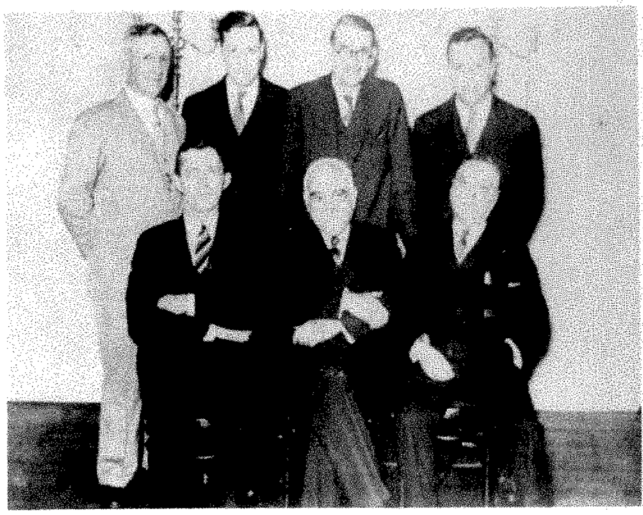

FIG. 4. Dr. Matas at the time of the presentation of the first Matas Award for Vascular Surgery. Seated at his right is Dr. Mont Reid, recipient of the first award. Others in the picture are Mike Hart, Dr. Lucian H. Landry, Dr. Emile Block, Dr. Isidore Cohn, and Dr. Alton Ochsner. (From Cohn I, Deutsch HB. Rudolph Matas. Garden City, NY: Doubleday and Co., 1960.

He was deeply concerned about our profession and one of his publications is entitled, "The Soul of the Surgeon," which appeared in the Transactions of the Mississippi State Medical Society in 1915. He spoke out strongly against quackery, fee splitting, and unnecessary surgery.

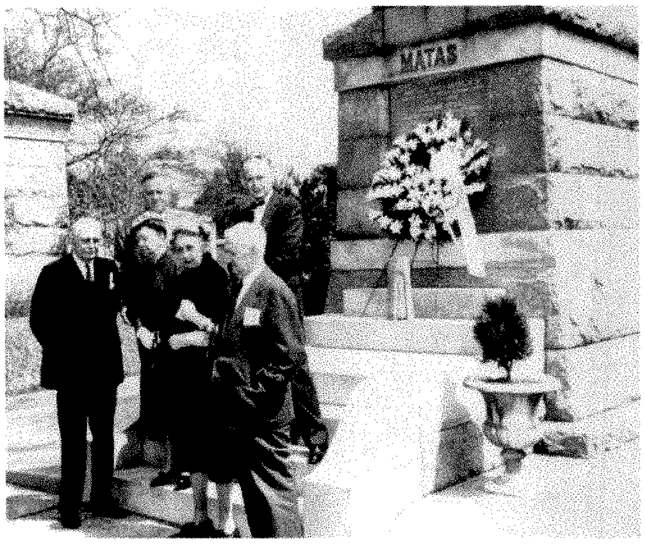

FIG. 5. A photograph of the Matas tomb during a meeting of the International Anesthesia Society in 1958. This meeting was dedicated to Dr. Matas. The individuals on the front row are Dr. Isidore Cohn, Mrs. M. C. Mehan, Mrs. Lucian (Bernice) Landry, and Dr. Lucian Landry. On the back row, Dr. Harold R. Griffith, and Dr. John Adriani. (From the private collection of Dr. Isidore Cohn, Sr., published with permission from Dr. Isidore Cohn, Jr.)

TABLE 1. *Significant Contributions of Rudolph Matas, M.D.*

1. Father of modern vascular surgery
   - a. First endoaneurysmorrhaphy
   - b. Treatment of an aortic abdominal aneurysm by wiring and electrolysis
   - c. Ligation of abdominal aorta
   - d. An aluminum band for compression of arteries
   - e. Emphasis on systemic effects of arteriovenous fistulae
   - f. Studies of venous disease
   - g. Emphasis of role of edema in erysipeloid infections
   - h. Classic paper on elephantiasis
   - i. Performed the first Kondoleon operation in the Western Hemisphere
2. First to use intravenous saline solutions in surgical patients
3. First to advocate gastric drainage with indwelling tube introduced through the nose
4. Laboratory studies on positive pressure respiration for open thoracic operations
5. Pioneer in local anesthesia
6. Contributions to the solution of the yellow fever problem
7. Use of motion pictures for instructional purposes

In all the study of the life of Rudolph Matas, only two negative comments were encountered. First, it was noted that he often failed to meet deadlines for publications set by others. For example, Dr. Cohn stated that the manuscript originally scheduled to appear in Volume I of *Keen's Surgery,* which was published in 1906, was finally sent in time for inclusion in the 5th edition, which was published in 1909. Dr. Matas was asked to prepare a history of medicine in the State of Louisiana in 1926. By 1948, Dr. Matas had accumulated a trunkful of documents and manuscripts, but had not completed the task because in preparing the material from Louisiana he found that this had to relate to medicine within the United States, and this had to relate to medicine in the world. This history was ultimately completed by a historian, Dr. John Duffy, who was employed by Dr. Matas, and was published in two volumes, Volume I in 1958, the year after Dr. Matas's death, and Volume II in 1962.[21] The second negative statement concerns his discussion at scientific meetings where the extent of his knowledge and understanding of a subject led to lengthy discussions that usurped the time of other individuals on the program.

TABLE 2. *Rudolph Matas: Elected Offices in Professional Societies*

President	New Orleans Medical and Surgical Association
President	Louisiana State Medical Society
President (Honorary)	Pan American Medical Congress
President	American Surgical Association
President	Southern Surgical Association
President	American Society for Thoracic Surgery
President	American College of Surgeons (Founding Member)
President	International Society of Surgery
Vice President	American Society of Clinical Surgery
Vice President	American College of Surgeons
Vice President	American Medical Association

Dr. Matas belonged to most of the major surgical associations during his lifetime, and held elective offices in many (Table 2).

Dr. Matas received 29 foreign decorations from Peru, England, Italy, Cuba, Denmark, France, Mexico, Poland, Venezuela, Belgium, and Greece, and 11 specific honors from Spain.

He was awarded honorary degrees from Washington University in St. Louis, The University of Pennsylvania, The University of Alabama, Tulane University, Princeton University, and the University of Guatemala. In fact, Cohn and Deutsch list 94 "degrees, honorary awards, foreign decorations, and official positions."

When I (GLJ) had the privilege of meeting Dr. Matas in New Orleans, he was 87 years old. He still attended functions held at Tulane University School of Medicine and it was apparent that the regard in which he was held by those audiences bordered on reverence. It was not unusual for Dr. Matas to enter the auditorium after the entire assemblage had gathered. On those occasions, Dr. Alton Ochsner would leave the podium, go to the rear of the auditorium, and personally escort Dr. Matas to his seat. As Dr. Matas proceeded down the aisle, the entire audience rose spontaneously and remained standing until Dr. Matas was seated. The support and adulation of the City of New Orleans for this great man was evidenced in the 1880s and continued through a 70-year period until his death in 1957.

He received ten local honors. One of these was the establishment of the Rudolph Matas Award in Cardiovascular Surgery through the Violet Hart Fund. This prestigious award has been given to only 11 surgeons in the past 53 years. Seven of these 11 recipients, including Drs. Mont Reid, Daniel Elkin, Alfred Blalock, Michael DeBakey, John Gibbon, Harris Muller, and John Kirklin, were members of the Southern Surgical Association. In 1954, Dr. DeBakey and Dr. Emile Holman were the last to receive the award from Dr. Matas personally, when Dr. Matas was 94 years old.

Dr. Rudolph Matas is the classic example of what an individual can accomplish based on his native intelligence, imagination, motivation, and energetic pursuit of his goals. During his boyhood, his family life was extremely unstable with the ultimate divorce of his parents, despite a strict Catholic religious indoctrination, and finally there was alienation from his mother and sister, who made active attempts to be destructive. His many moves during childhood provided a poor climate for developing close friends. Some of the schools he attended were not stimulating, and had he not had his own insatiable desire to read and to learn, he might have been poorly educated. His family's financial position varied greatly from time to time, his father at times being successful in some of his investments and establishment of a practice, while at other times he was financially disadvantaged. While a medical student, his roommate, one of his closest friends, died within 24 hours after being stricken by yellow fever, despite Dr. Matas's extensive experience with this disease. He was unable to marry the girl he loved for many years, because she was married to another man, and even subsequently, when she was separated from her husband, their religion delayed their marriage. Their one child was stillborn and his wife preceded him in death by many years.

He was an extraordinary individual despite all of these negative influences. He was recognized by some internists as the best diagnostician in America, and according to Cohn, was the best surgeon of his time by Dr. Crile. He was a superior teacher. He loved his patients, and in return he was loved by his students and those with whom he came in contact, both socially and professionally.

The greatness of Rudolph Matas is eloquently expressed in statements by Dr. J. W. Lipscomb in 1915 and in a birthday volume produced in his honor in 1931:

> "The foremost man in the foremost college in this great Southland of ours, the Nestor of our brilliant and gifted profession. We have but to mention his name and his contemporaries throughout the United States stand at attention. Someone has said that, to be an ideal doctor, we must possess the wisdom of Solomon, the faith of Abraham, the meekness of Moses, the patience of Job, the charity of Dorcas, the eloquence of St. Paul, the bravery of Joshua, the strength of Samson, the executive ability of a Jezebel, must be a hunter like Nimrod, a fisher like Peter, a climber like Zaccheus, a driver like Jehu. He should be free of Asa's gout, the melancholy of Saul, the gastric infelicity of Timothy; have all the virtues of the most virtuous and the religion of all saints. All of these are his."[22]
>
> "He is a rare mixture of the Old World and the New. He is a citizen of the World. He is a towering figure in the world of medicine and of men. He has proved himself to be a chivalrous knight and at once a humble worker, a literateur, a dreamer, an original thinker and a thorough master of the art of surgery. His ways are modest, his motives pure."
>
> "When the influence of many of us will be scattered as grains of sand by the wind, Dr. Matas's influence will be as a beacon light across the storm-tossed sea in the life of many men. The rays of this light will continue to carry the message of devotion to duty, love of mankind, mercy to the needy and sick, and humility."[1]

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The Role of Gynecologic Surgeons in the Southern Surgical Association

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GYNECOLOGISTS have played a major role in the development and history of the Southern Surgical and Gynecological Association. A review of the Transactions over the past 100 years supports this statement. The organization of this Association was primarily the result of the foresight and energies of two young brothers, W. E. B. Davis and J. T. S. Davis, of Birmingham, Alabama. After completion of medical school in Nashville, Tennessee, the brothers returned to Birmingham in 1886. On December 15, 1886, the brothers formed a new state organization, the Alabama Surgical and Gynecological Association. H. N. Rosser was elected President and W. E. B. Davis was elected Secretary. Fifty leading surgeons of the state were invited to join.

In 1887, the brothers proposed that a broader organization be formed out of the Alabama Surgical and Gynecological Association, to be named the Southern Surgical and Gynecological Association. Representative surgeons from throughout the South were to be invited to join.

Surgery in the South

In the nineteenth century, surgery, especially gynecologic surgery, developed rapidly in the southern states. Knowledge of successful operations spread over this country and Europe. The demonstration that complicated operative procedures could be performed with low mortality resulted in a wide interest in surgical diseases in the abdomen.

The development of gynecologic surgery in the United States was stimulated by the dramatic contributions of Ephraim McDowell in Kentucky (1809) and J. Marion Sims in Alabama (1849).

In 1809, Ephraim McDowell,[1] in his home in Danville, Kentucky, removed a 22.5 pound ovarian cyst from Jane Todd Crawford. This successful operation, and 12 more to follow for ovarian tumors, signalled the beginning of abdominal surgery. For many years thereafter, laparotomy was performed principally for the removal of large ovarian cysts. Several surgeons in this country, especially the Atlee brothers of Philadelphia, and others in England (Lawson Tait and Spencer Wells) became famous after reports of large series of successful operations for ovarian cysts.

It is entirely fitting that the Southern Surgical Association chose to use a bust of McDowell as the central figure in its organizational insignia, which first appeared in Volume II of its Transactions for the year 1889.

In Montgomery, Alabama, J. Marion Sims[2] (1813–1883) reported the surgical cure of a patient with vesicovaginal fistula, a condition that had defied all previous surgical attempts to correct. Subsequently, Sims developed many other operative procedures, established the Women's Hospital in New York, and became famous as a surgeon in the capitals of Europe. He was especially interested in the surgical treatment of pelvic cancer. Because the disease often was considered contagious and likely venereal, and because Sims continued to treat pelvic cancer in the Women's Hospital of New York, he was removed from the staff at the insistence of the Board of Lady Managers, although he had been instrumental in the building of that hospital. This was a dramatic and historic confrontation.

Presented at the 100th Anniversary Meeting of The Southern Surgical Association, Hot Springs, Virginia, December 6–9, 1987.

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The accomplishments of the early intrepid surgeons remain a source of great pride to Southerners. Distinguished southern surgeons included Dudley, Eve, Emmett, and others.

Robert Battey,[3] (1828–1895) in Rome, Georgia, performed laparotomies for excision of ovaries in many patients from 1872 to 1893. His indications for oophorectomy are not acceptable currently. They included neurasthenia, headaches, mental problems, and insanity. His techniques were excellent and advanced the safety of laparotomy for other purposes, especially for various adnexal diseases. He also championed the vaginal approach for removal of the ovaries. He was an expert anatomist. He was President of the American Gynecological Society in 1899 but was never a member of the Southern Surgical Association.

Organizational Meeting October 12, 1887

The need for specialty surgical associations to disseminate information and to allow comparison of results among surgeons was evident by the end of the century. It was time for the birth of the Southern Surgical and Gynecological Association.

FIG. 1. Ephraim McDowell, forerunner of abdominal surgery, 1809.

James Marion Sims.

FIG. 2. J. Marion Sims, cure of vesicovaginal fistula, 1849, Gynecologic Surgeon from Montgomery, Alabama.

The mission of the proposed Southern Surgical and Gynecological Association was "to quicken the search and diffuse knowledge in relation to surgery and gynecology in the southern states." W. D. Haggard, Professor of Obstetrics and Diseases of Women in Nashville, advised his former student, W. E. B. Davis, that gynecology should be included. Davis described this undertaking in his presidential address in 1902.

> "When it was decided by some of the leaders of the Alabama Association to extend the organization, the honorary members were conferred with and they, with but few exceptions, approved of the plan. I remember that Dr. Yandell wrote me that he thought the union would prove rather an unsatisfactory one, as the general surgeon would not enjoy listening to a gynecologist discuss dysmenorrhoea, and the gynecologist would have very little interest in the treatment of a fracture of the thigh. Yet with so great a surgeon speaking disparagingly of it—and this was the first association where the surgeons and gynecologists were combined in this way—its name has anticipated what may be expected in the future. Indeed, purely gynecological societies will prove less frequent with each recurring year. After conferring with a large number of the members of the new organization, a letter signed by the President and Secretary was sent to representative men throughout the South, inviting them to attend the approaching meeting of the

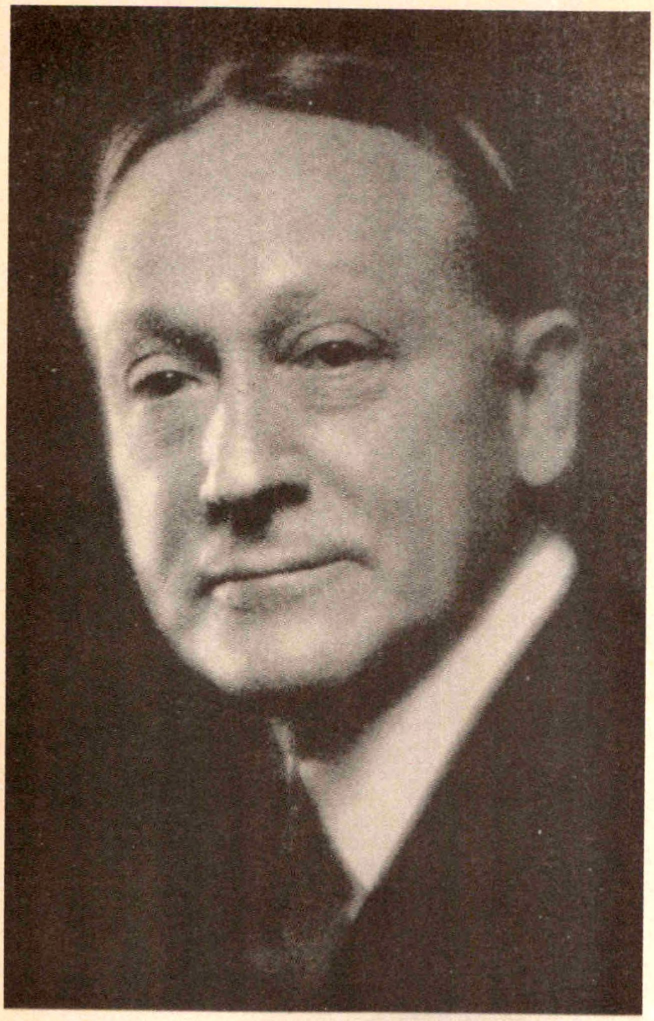
William David Haggard, M.D.

FIG. 3. W. D. Haggard, Professor of Obstetrics and Diseases of Women, University of Tennessee, Nashville.

> Alabama Surgical and Gynecological Association, October 11 and 12, 1887, with a view of forming the Southern Surgical and Gynecological Association. They were asked to express their opinion of such an organization and to signify whether they would be willing or not to be placed upon its roll of members. There were about eighty favorable replies to these letters. Among those who expressed very great enthusiasm to see the organization as a truly representative Southern special society was W. D. Haggard, of Nashville, the father of our Secretary. He was very active in his efforts in behalf of the proposed organization. Indeed, his services were of inestimable value in the early history of the organization."

The organizational meeting was completed on October 12, 1887, despite the antagonism of some members of the Alabama Society. The Davis brothers had invited the southern members of the American Surgical Association (founded in 1880) and the American Gynecological Association (founded in 1876).* In addition to these, certain other prominent physicians were invited to the meeting in Birmingham. Only a few attended but 80 wrote letters of interest. The broad invitations later proved a source of embarrassment to the Secretary who had invited into membership physicians who were important, but many of whom were neither general surgeons nor gynecologists. However, the result was the enthusiastic formation of the new Association. W. D. Haggard was elected President and W. E. B. Davis was elected Secretary.

First Annual Meeting

At the first annual meeting of the Southern Surgical and Gynecological Association in Birmingham, on December 4, 5 and 6, 1888, 41 members and 50 visitors were present. W. E. B. Davis read a synopsis of the published minutes of the organization meeting of the previous year. Eighteen presentations were made at the first annual meeting, of which seven were related to gynecology and eleven to general surgery. Included were the following: (1) "Chronic Pelvic Cellulitis," (2) "The Medical Treatment of Fibroid Tumors of the Uterus," (3) "Floating Kidney, with Vicarious Menstruation," (4) "The Present Status of Electro-Therapeutics in Gynecology," (5) "Hysterectomy in Cancer of the Uterus," (6) "Laceration of Perineum and Rectocele," and (7) "Treatment of Certain Forms of Menorrhagia, with report of Cases."

The first President, W. D. Haggard (1888), was influential in forming and setting the course of the Association. His son, W. D. Haggard, Jr., was Secretary from 1901 to 1918, when he became President. The younger Haggard guided the Association with great foresight during his tenure as Secretary.

The Senior Haggard's Presidential Address (1888) stated:

> "Gynecic Surgery, with all its brilliant achievements, owes its present exalted position to the illustrious Sims, no less than Abdominal Surgery owes its origin to the world renowned McDowell. The outcome of the labors of these two remarkable men in beneficent results has no parallel in the annals of medicine. They conferred on America the honor of being the birthplace of Gynecology, and did more to alleviate the sufferings, restore the health and prolong the lives of women than any two men living or dead." . . .
>
> "The Southern Surgical and Gynecological Association did not spring voluntarily into existence, but was the outgrowth of necessity and the embodiment of unknown power."
>
> "It was the work of a few energetic minds and hearts that saw its need, and seized the opportunity to give it form and being, which was accomplished in this city the second Tuesday in September 1887, at a most auspicious moment, and under most favorable circumstances." . . .
>
> "This Association has now met for the first time since its organization to lay the offerings of another year's work on the altar of science, and to further consider the present state of surgery and gynecology, and to contribute its mite in promoting the advance-

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* The 100th anniversary of the AGS was held in The Homestead Hotel, Hot Springs, Virginia, May 24–29, 1976.

> ment of each department as a pure science, and their perfection as practical arts."
>
> "None, perhaps, will question the supreme and commanding fact that in these two branches of medical science the greatest advances have been made."

Three classes of professional men were wanted for this Association: first, the specialist (a surgeon or gynecologist of distinction, skill, and experience); second, the general practitioner of eminence and experience, who in addition, practiced surgery and gynecology to a limited extent; and third, the young surgeon and gynecologist of character, talent, education, and promise, but whose practical experience was limited. In this connection, the term "promise" was considered most important.

At the conclusion of the first regular meeting in 1888, Hunter McGuire, of Richmond, Virginia, was chosen as President. His reputation was outstanding throughout this country and in Europe. During the War between the States, he was Medical Director of the Army of the Shenandoah under General Stonewall Jackson. He had been President of the American Surgical Association and American Medical Association. His selection as President was the rallying point to make the new organization a viable one.

Meetings 1888 to Date

The second session of the Association was held in Nashville, Tennessee, November 14–18, 1889. There were 19 presentations of which 14 were related to gynecologic surgery. There were five papers on general surgery.

At the third meeting of the Association in 1890, Lewis S. McMurtry, Professor of Gynecology at the University of Kentucky in Louisville, delivered a long paper entitled "Inflammation In and About the Head of the Colon." He discussed in detail the problems of appendicitis and the treatment by laparotomy. There was prolonged discussion. McMurtry was elected President of the Association for the coming year. Of 18 papers presented at this meeting, seven were on gynecologic subjects.

The following year, 1891, in his Presidential Address, McMurtry stated that within 15 years the entire practice of surgery had been revolutionized. New methods had been introduced and new regions invaded. The science and art of gynecology, which a few years previously was limited to a small and narrow field, had grown into a major branch of medical science. Formerly, it had been divided between midwifery and surgery, as a minor branch of one or both, but in recent years gynecology had become an independent and essential specialty.

McMurtry entered a protest against the perversion of the word "conservatism" when it was used to oppose and retard progress in surgery, the supreme purpose and object of which is "to preserve in a safe and entire state, or from loss, waste or injury." He stated further that one of the great advances of modern times is the knowledge acquired of the inflammatory diseases of the uterine appendages. More than a quarter of a century previously, two Frenchmen, Bernutz and Goupil, had described these lesions and their deadly effects.

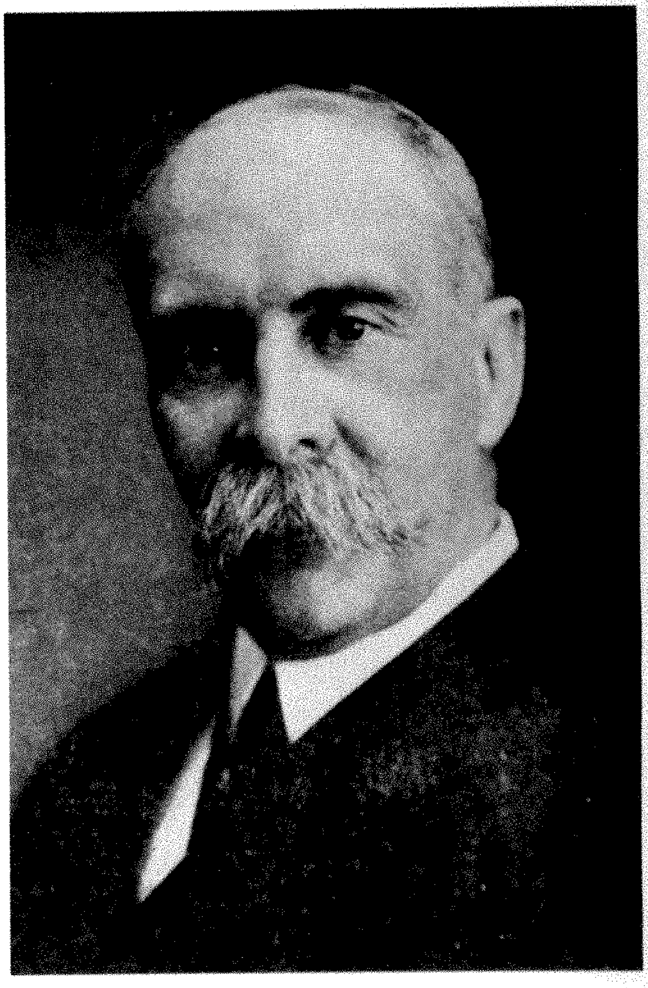


FIG. 4. L. S. McMurtry, Professor of Gynecology, Louisville, Kentucky.

At that time (1891) there were 130 members of the Association, of whom 30 were gynecologists. Of the 23 presentations, 11 were on gynecologic subjects.

At the seventh meeting in 1894, in the Presidential Address, Cornelius Kollock stated, "Our Association has the advantage of combining two specialties, surgery and gynecology. For the country doctor, away from large communities, the knowledge of both is almost imperative. In cities, gynecologists and surgeons may supplement each other's work, but in the country, the doctors cannot always go in pairs. Let our young physicians, especially those who seek a country practice, strive for the knowledge of both specialties; then there will be less

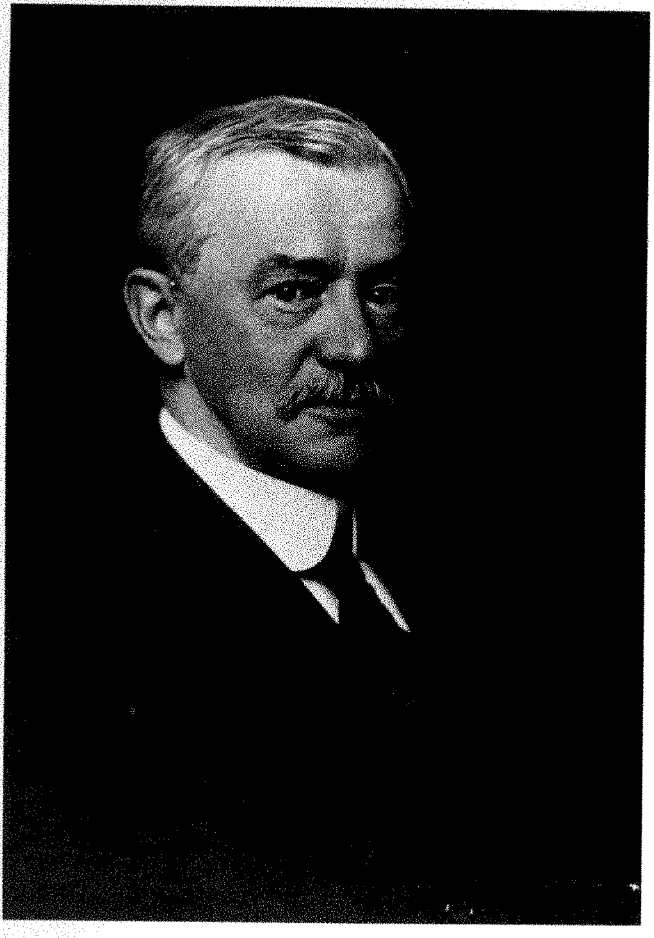


FIG. 5. Howard A. Kelly, Professor of Gynecology, Johns Hopkins.

of the murderous practice of craniotomy and a more sacred regard for the preservation of life."

There were eight papers on gynecology and thirteen related to general surgery at the 1894 meeting. In 1895 there were 17 presentations, seven of which were on gynecologic subjects.

At the ninth meeting of the Southern Surgical and Gynecological Association in Nashville, in 1896, there were 17 reports on the program, of which three related to gynecology. "Vaginal versus Abdominal Section for Pus in the Pelvis" by William D. Haggard, Jr., provoked extensive discussions by Joseph Johnson, Charles Noble, Howard A. Kelly, L. S. McMurtry, R. B. Maury, and W. E. B. Davis. This was an in-depth review of the use of colpotomy and vaginal hysterectomy for the treatment of severe inflammatory diseases in the pelvis. These approaches had been recommended especially by French surgeons, including Doyen, Segond, Pozzi, and others.

Many of the members were always active discussants. Howard A. Kelly, professor of gynecology at Johns Hopkins, was one of the most active members of this Association, frequently presenting papers and often discussing others.

In 1897, there were 19 presentations, six on gynecology and 13 on general surgery. In 1898 there was a total of 17 reports, six on gynecology and 11 on general surgery.

At the twelfth meeting in 1899, President Joseph Taber Johnson, Professor of Gynecology at Georgetown University, spoke as follows:

> "The union of surgery and gynecology in our Association has done much to bring together the men devoting their lives to these two great departments of medicine, and may possibly do much more in the coming century to wipe out the lines of demarkation which now separate them."

Johnson further stated that the revolutionary operation of the intrepid Kentucky surgeon, Ephraim McDowell, constituted a very pleasant union of marriage of surgery and gynecology. He noted that the Southern part of our country had furnished many noted surgeons and gynecologists to the medical profession.

Johnson continued:

> "The practice of surgery and gynecology brings our membership very near together, and it is not at all impossible as the signs of the times are interpreted, that gynecology, as a separate and separated specialty, may gradually cease to exist as such, and become absorbed into the larger and more general department of surgery."
>
> "It is very difficult to say where the office of the gynecological surgeon leaves off and where that of the general surgeon begins . . . who knows but that in the evolution of events, the general surgeon and the gynecologist may soon lie down together, and a little child may lead them."

By 1900, there were 150 members of the Association, of whom 22 were gynecologists. Of 22 presentations, seven were on gynecologic subjects. At the 1901 meeting, 24 papers were presented and nine were on gynecologic subjects.

At the 28th session, in 1915, Thomas S. Cullen, Professor of Gynecology at the Johns Hopkins School of Medicine, gave a lengthy Presidential Address. He discussed the status of hospitals, the trained nurse, education, art and medicine, the beginning of radiation therapy and the importance of pathology. At this meeting in 1915, he stated:

> "After trying to analyze the secret of the success of this Society, I have come to the conclusion that its method of organization, namely, the divorcing of the scientific from the business sessions, has been an important factor. Then it seems that all of our members who take part in the proceedings aim to save their best work for these gatherings, but the most important of all is the fact that in the selection of the members such great care has been exercised that there is rarely, if ever, a discordant note. This Society is really the clearing house for the year's work, and the stimulus obtained at these meetings is of lasting value. If the Councils in the future select as wisely as they have done in the past, this Association will have an ever increasing sphere of usefulness. . ."

The report of the Council on December 14, 1915, recommended that a Committee of three, consisting of Stuart McGuire, Chairman, J. W. Long, and J. M. T.

Finney "be appointed to report on the best method of rendering the list of members more elastic, to recommend any immediate changes in the Constitution and By-Laws, and to consider the question of dues and suggestions to the Committee from the members."

At the conclusion of the meeting in 1915, Cullen, the recent President of the Association, was elected to the Council, as was the custom. The following year at the 29th annual business meeting of the Association at White Sulphur Springs, West Virginia, on December 13, 1915, the report of the Council included the following:

> "The Council endorses and recommends the following changes in the Constitution and By-Laws of the Southern Surgical and Gynecological Association, this being the report of the special Committee composed of Stuart McGuire, Chairman, John W. Long, and J. M. T. Finney, who were appointed at the previous meeting:
>
> 1. C: Change the title from the Southern Surgical and Gynecological Association to the Southern Surgical Association and change the word 'Member' to 'Fellow' and 'Membership' to 'Fellowship' wherever they occur in the Constitution and By-Laws."

This proposal was accepted by the Association.

It may appear surprising at first that the Committee, named by the Council during the presidency of T. S. Cullen, should recommend omission of "Gynecological" from the name of the Association, since Cullen was such a prominent gynecologist in this country, and was known widely over the world. Perhaps this is explained by understanding Cullen's philosophy. He stated frequently that trainees in gynecologic surgery should be able to care for any surgical disease within the abdominal cavity when found at the time of laparotomy. Secondly, he insisted that the training of gynecologic surgeons and general surgeons should include special training in pathology, both in general pathology and that related to a specialty. The 5 years of training in gynecologic surgery in the Johns Hopkins Hospital under Cullen were interspersed with surgical experiences with the General Surgical Service. In addition, one full year in general pathology was followed by a second year in gynecologic pathology, the latter while assisting in surgical operations. Cullen arranged a continuous relationship with the Department of Pathology throughout the training of each resident. Cullen's predecessor, Howard A. Kelly, had instilled the necessity of training in pathology.

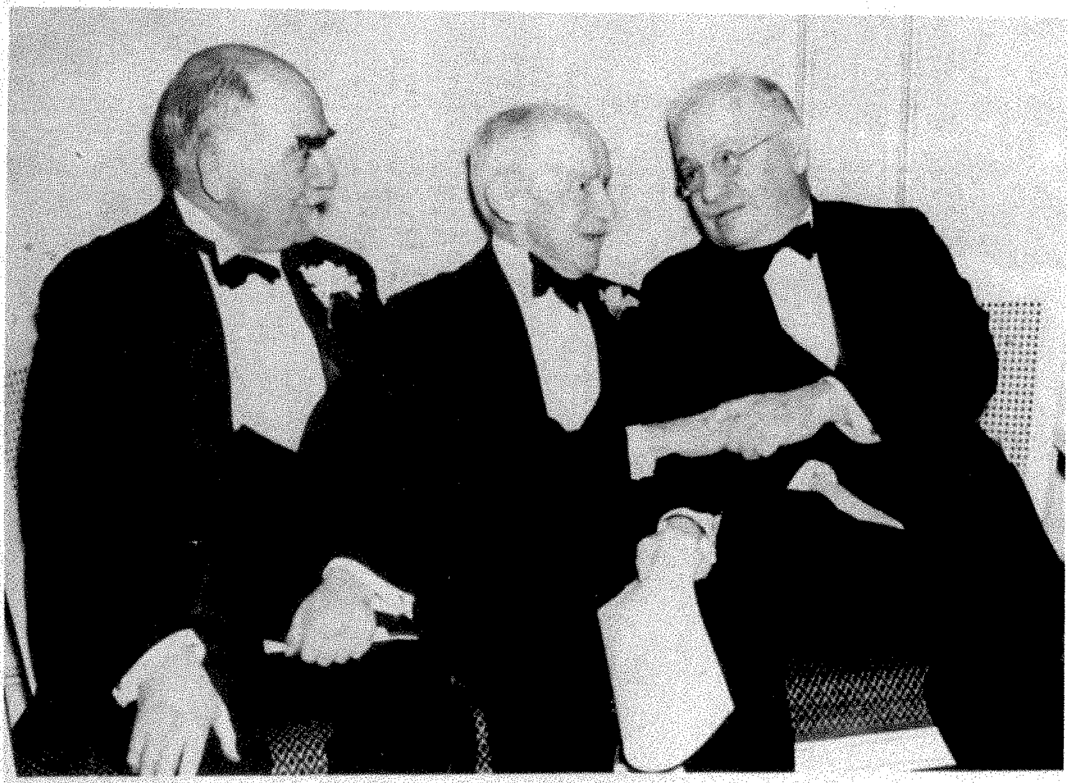
I believe that Cullen's opinions must have been received well by this Committee which recommended change of the name of the Southern Surgical and Gynecological Association to the simpler and more concise form, "The Southern Surgical Association." After the name change, contributions from gynecologists diminished through the years. Was this name change a factor in the decrease in activity of the gynecologists? Likely it was related to increasing technological factors in each specialty and the increasing number of medical organizations.

FIG. 6. Thomas S. Cullen, President 1915, Professor of Gynecology, Johns Hopkins.

When I was his resident, Cullen expressed to me his opinions of the Southern Surgical Association on a number of occasions. He stated that this was the leading surgical association in the world, that the members saved their best work for the annual meetings, that the fellowship was unexceled, and that its influence was important for American surgery. He also indicated that he would be pleased if I were a member some day.

Gynecological presentations numbered three in 1916, four in 1917, seven in 1918, five in 1919, nine in 1920, and five in 1921.

In his presidential address in 1922, C. Jeff Miller, Professor of Gynecology at Tulane, reviewed the scientific advances in surgery during the 20 years preceding the organization of the Southern Surgical and Gynecological Association. Intense efforts had ushered in knowledge of cellular pathology, primary wound healing, fermentation, immunology, and bacteriology. Only 5 years before the origin of this Association, Lister had announced his methods of antisepsis in surgery which



Thomas S. Cullen Howard A. Kelly

FIG. 7. Tom Cullen, Howard A. Kelly, J. M. T. Finney, at Cullen's 70th birthday celebration, 1934. Three Presidents of the Southern Surgical Association: two gynecologists and one surgeon.

led to aseptic surgical techniques (1895). The Pasteur Institute was founded in Paris in 1888, 1 year after the Southern Surgical Association. Miller indicated that hospital standards, surgical indications, and results had improved.

At the 1922 meeting, 38 papers were presented, of which only two were related to gynecology.

In 1927, President Guy L. Hunner of Baltimore summarized his concepts of ureteral stricture and urinary stones. He emphasized the importance of the work of Kelly in female urology. Thirty-seven papers were presented, including only three on gynecology. Thereafter, gynecologic presentations continued to decrease in number (Table 1).

In 1929, President Lucius E. Burch, Professor of Gynecology at Vanderbilt University, made a strong recommendation that residents in gynecologic surgery should have 5 years in training. The first year should be devoted to internal medicine, the second to pathology, and the next 3 years to the operating room, laboratories, and the wards. He did not include obstetrical training in his recommendations for the training of a gynecologist. In 1929, six of 35 presentations related to gynecology.

At the 1954 meeting, President John C. Burch, son of Lucius Burch and Professor of Gynecology at Vanderbilt University, advised that strict standards of pelvic surgery include . . . "the conservation of useful function." He indicated that improvement in surgical training programs was needed.

At the 1980 meeting, President Laman A. Gray, Sr. of Louisville recommended that the pelvic surgeon or gynecologist have additional training in general surgery, to include intestinal surgery, urologic surgery, hepatobiliary, and intra-abdominal vascular surgery.

Evolution

The American Gynecological Society (founded in 1876), consisting of both gynecologists and obstetricians, was the most influential voice in its field until the past two or three decades. Their meetings were impressive. Amalgamation with the American Association of Obstetricians and Gynecologists diluted its prestige and the luster of its early years has faded.

The formation of the Society of Pelvic Surgeons in 1952 by Joe V. Meigs, of Boston, member of the Southern Surgical Association, has had a stimulating influence on surgical gynecology. Its 150 members, mostly from this country, but with representatives from many countries, have placed much emphasis on the advancement of surgical techniques in gynecology, urology, and general surgery in the pelvis. In recent years, the American College of Surgeons and the American College of

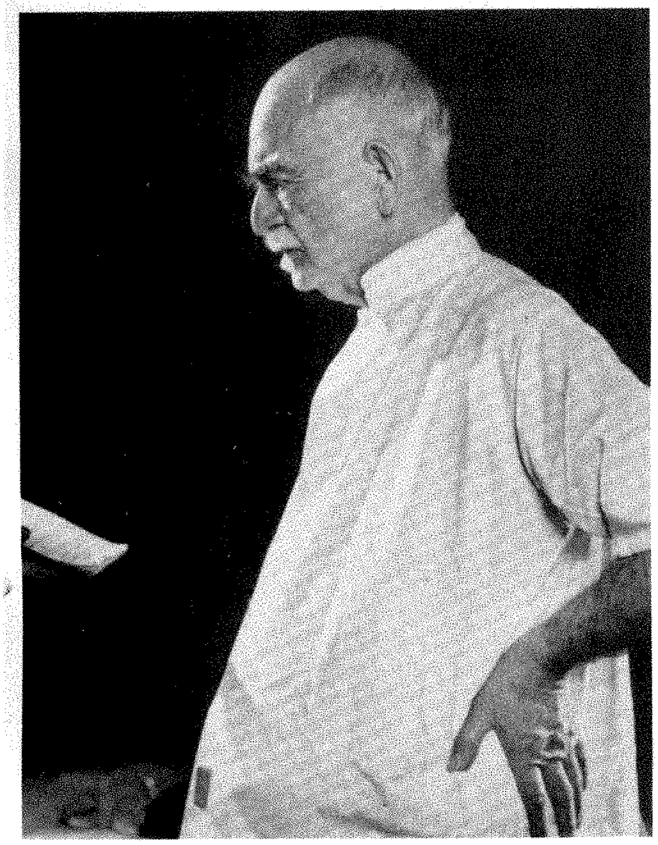


FIG. 8. Cullen in the operating room. Karsh, Ottawa.

FIG. 9. John C. Burch, Professor of Gynecology, Vanderbilt, President 1954.

Obstetricians and Gynecologists have emphasized increasingly the need for detailed surgical training in gynecology.

The interest in gynecologic oncology and the appearance of the subspecialty Board of Gynecologic Oncology

TABLE 1. *Gynecological and General Surgical Presentations: 1888–1916*

Years	Gynecological	Surgical	Totals
1888–1889	21 (56.8%)	16 (43.2%)	37
1890–1899	67 (34.5%)	127 (65.5%)	194
1900–1909	66 (22.4%)	228 (77.6%)	294
1910–1916	30 (11.4%)	234 (88.6%)	264
Totals 1888–1916	184 (23.3%)	605 (76.7%)	789
Name Changed To Southern Surgical Association in 1916: 1917–1986			
1917–1926	47 (13.4%)	305 (86.6%)	352
1927–1936	38 (9.7%)	352 (90.3%)	390
1937–1946	23 (6.8%)	313 (93.2%)	336
1947–1956	24 (5.8%)	391 (94.2%)	415
1957–1966	19 (4.4%)	416 (95.6%)	435
1967–1976	13 (3.3%)	386 (96.7%)	399
1977–1986	6 (1.7%)	341 (98.3%)	347
Totals 1917–1986	170 (6.5%)	2504 (93.6%)	2674
Grand totals	354	3109	3463

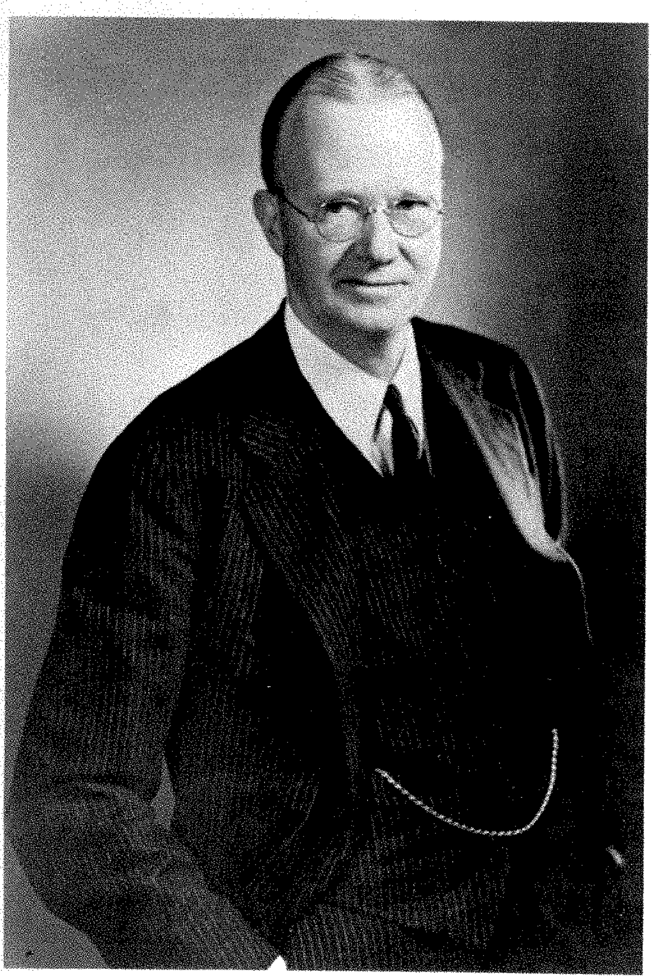


FIG. 10. Joe V. Meigs, Professor of Gynecology, Harvard. Founder of the Society of Pelvic Surgeons.

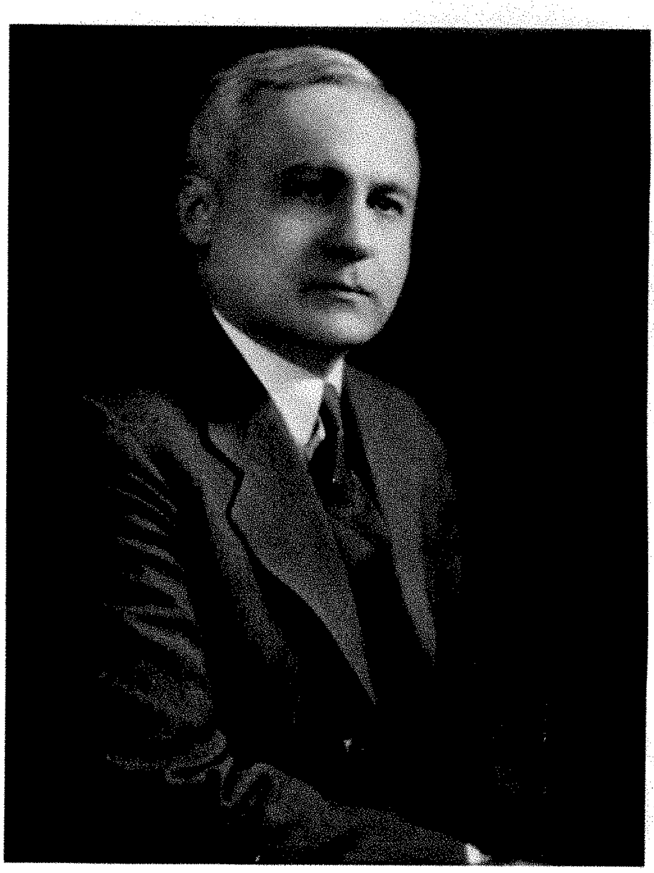


FIG. 11. Emil Novak, Professor of Gynecology, Johns Hopkins: one of the prolific contributors.

have stimulated post-residency surgical training programs. This has improved the quality of pelvic surgery.

In the early years of the Association, the number of presentations devoted to gynecologic topics varied from 57 to 11%, averaging 23% of the total. This has decreased to 1 or 2% in recent years (Table 1). Probably the principle reasons for the decrease in the number is that fewer gynecologic surgeons have been elected to membership in the Southern Surgical Association over the past 30 years. Over that period more than a dozen distinguished gynecologist members have died. These include Joe V. Meigs, Langdon Parsons, Lucius Burch, John Burch, Curtis Tyrone, Glenn Craig, Walter Holmes, J. M. Hundley, Jr., Emil Novak, W. T. Black, Lawrence Wharton, E. H. Richardson, Frank Whitaker, and others. Also, in the past 20 years, only one gynecologic surgeon has been admitted to membership. In the first 50 years, ten presidents were gynecologists. In the second 50 years, only two were gynecologists.

Developments in cardiovascular surgery have stimulated the admission of many of those able specialists who have presented frequent dramatic reports. It is evident that many subspecialties have become so highly specialized that the gynecologic surgeon cannot find any application in his own field. Abdominal surgery and gynecologic surgery should have a closer relationship than any other subspecialties.

The importance of the inclusion of general surgical training in the education of the gynecologic surgeon and the pelvic surgeon is being accepted increasingly in training programs. The general surgeon, certainly the abdominal surgeon, likewise will benefit from exposure to gynecologic surgery. The relationship should be nurtured.

Gynecologists have had a strong commitment to the Southern Surgical Association since its founding. It is to be hoped that they will have the opportunity and find the stimulus to continue their contributions through the next century.

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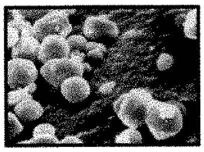

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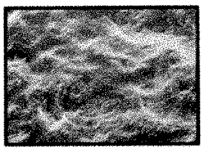

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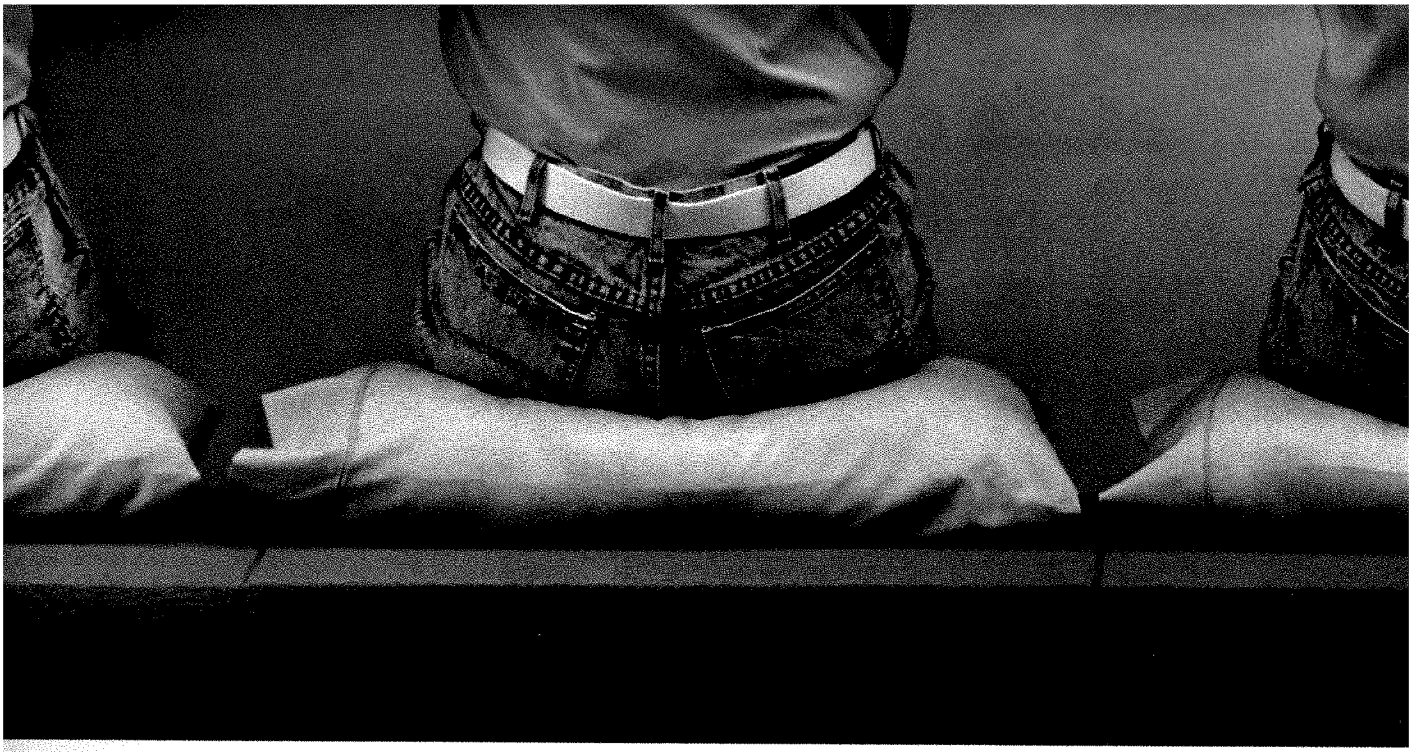

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INDICATIONS AND USAGE: Topical corticosteroids are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.
CONTRAINDICATIONS: Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.
PRECAUTIONS: ***General:*** Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia and glucosuria in some patients. Conditions which augment systemic absorption include the applications of the more potent steroids, use over large surface areas, prolonged use and the addition of occlusive dressings. Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area and under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids. Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See PRECAUTIONS—Pediatric Use.) If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted. In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.
Information for the Patient: Patients using topical corticosteroids should receive the following information and instructions: 1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes. 2. Patients should be advised not to use this medication for any disorder other than for which it has been prescribed. 3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician. 4. Patients should report any signs of local adverse reactions especially under occlusive dressing. 5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.
Laboratory Test: The following test may be helpful in evaluating the HPA axis suppression: ACTH stimulation test
Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids. Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.
Pregnancy Category C: Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women of teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.
Nursing Mothers: It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities NOT likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when any topical corticosteroids are administered to a nursing woman.
Pediatric Use: Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio. Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches and bilateral papilledema. Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.
ADVERSE REACTIONS: The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximately decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, miliaria.
OVERDOSAGE: Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects. (See PRECAUTIONS.)
DOSAGE AND ADMINISTRATION: Topical corticosteroids are generally applied to the affected area as a thin film three or four times daily depending on the severity of the condition. Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions. If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted.
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Three, after two initial negative tests one year apart, get a procto exam every three to five years if you are over 50.

These guidelines are the best protection against colorectal cancer you can have.

If you're not over 50, please give this information to friends and loved ones who are.

In any case, please help spread the word.

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Honorary Fellows of the First Century

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HONORARY MEMBERS are mentioned in the first meeting, Volume 1 of the Transactions of the Association for the Birmingham, Alabama meeting of December 1888. Unfortunately, the comment is a negative one, since Article XV of the By-Laws reads: "By-Laws Article XV. No Honorary Member shall be placed upon the roll of this Association." The very fact of this inclusion in the original By-Laws indicates there must have been some discussion about the possibility of Honorary Membership from the beginning of the Association.

Throughout the *Transactions* there is considerable confusion regarding the status of Honorary Members, their qualifications, their numbers, and the status of the Constitution and By-Laws with regard to them. For many of the Honorary Members elected from overseas, there is no indication that they ever attended any meeting, that they sent letters regretting their inability to attend, or even any indication that they accepted the Honorary Membership that had been conferred on them. Some of the confusing situations probably are related to the changing status of the organization, the change in location of the secretarial office, and the inertia that accompanies any organization with respect to the printed word which is its bible.

Volume II, 1889, has a listing of members and identification of those who are "Founders," but the status of Honorary Membership is unchanged.

Volume III, 1890, lists Members, "Founders," and lists the year that Members were elected, but there have been some changes in the By-Laws. Two By-Laws have been deleted and the article prohibiting Honorary Members is now Article XIII, but the wording is unchanged.

Volume VI for 1893 includes a note in the minutes for Thursday, November 16, 1893, which reads as follows: "It was moved to revoke By-Law XIII, and to provide for Honorary Members in foreign countries limited to ten. (To lie over one year)."

By the meeting of 1894, recorded in Volume VII, it is clear there has been a change in the sentiment of the members as the Report of the Council given on Thursday, November 19, 1894, includes the following: "A resolution was passed to recommend to the Association the adoption of the resolution offered at the last meeting to elect the number of Honorary Members to the number of ten, placing the limit at that number, beginning with the election of five at this session. Viz: S. Pozzi, of Paris; A. Martin, of Berlin; George Foy, of Dublin; Charles Jacobs, of Brussels; and O. Morisani, of Naples." None of these are listed in the roster of Members and there is no separate listing of Honorary Members nor is there any indication that any of these five attended the meeting. As a matter of fact, as one reviews the list of Members and guests attending the meetings, no overseas Honorary Member ever attended any of the meetings until 1978.

Volume VIII, 1895, lists alphabetically on a separate page preceeding the usual roll of Members, the five Honorary Members elected in the previous year. It is of interest that the Honorary Members are identified only by name and city of origin without any of the information regarding their academic or other activities as is the case for Members. Furthermore, there is no indication in this or the preceeding volume regarding how these

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five individuals were selected, who proposed them, or what their contributions were to the Association or to surgery in general. This style of listing the Honorary Members is continued until Volume XLI where the last name is that of the most recently elected Honorary Member, but others are still in alphabetical order. From this point on, names that are added are placed in chronological order, but those listed through 1917 remain in their alphabetical sequence. Volume XLVIII, 1935, places everyone in alphabetical order. Volume LX, 1948, is part chronologically and part alphabetically arranged. Volume LXV, 1953, is arranged completely in chronological order. Volume LXXXII, 1970, has everyone in alphabetical order and this sequence is continued until the present time.

It is of interest that Volume VII, which contains the minutes regarding the election of the Honorary Members and also a separate roster listing them, did not delete the article in the By-Laws, which prohibited their membership. Volume VIII eliminates Article XIII and also includes a change in the Constitution, which was not recorded in the previous year. Section 2, Article IV of the Constitution reads as follows: "The Honorary Member shall not exceed 10 in number, and shall enjoy all the privileges of other Members, excepting to vote or hold office, but shall not be required to pay any fee."

There is no change in the status of Honorary Members, their listing, the Constitution, By-Laws, or anything else related to Honorary Membership until Volume XV where the Report of the Council for November 13, 1902 includes the following: "As Honorary Members, the Council nominates: Dr. Thaddeus A. Reamy, of Cincinnati, Dr. J. McFadden Gaston, of Atlanta, and Dr. Richard B. Maury, of Memphis, Tennessee."

It is interesting to note that all three of these are from the United States, whereas the original intention had been to elect up to a maximum of 10 foreign members. At least two of the newly elected Honorary Members had been Members of the Southern before this time but there is no listing of Dr. Maury in the membership and, once again, the Honorary Members are listed before the Members with no additional identification. Dr. Gaston continues to be listed in the regular membership file, in addition to being listed as an Honorary Member, whereas Dr. Reamy is listed only as an Honorary Member and not under the regular membership listing. There is nothing in the minutes to indicate when the decision was made to allow the election to Honorary Membership of either individuals practicing in the United States or of individuals who had prior membership in the Southern.

In Volume XVI, 1903, there is the first notice of the death of an Honorary Member. Dr. J. McFadden Gaston is one of the Members of the Southern who had been elevated to Honorary Membership and his death is recorded also in the membership list where his name is still present. There is a three-page signed memorial preceeded by a full-page picture.

The next addition to the list of Honorary Members is recorded in Volume XX, 1907, where Dr. L. M. Tiffany of Baltimore appears as an Honorary Member. In the Transactions for the previous year, Dr. Tiffany is listed as a Member but in this volume his listing is only under the group of Honorary Members without any further identification. This is particularly surprising since the list of officers on the preceeding page indicates he was President in 1895.

In the Report of Council for December 19, 1907, item 2 reads, "The Council recommends that in Section 2 of Article IV of the Constitution, in reference to Honorary Members, that the word 'twenty-five' be substituted for 'ten' and that Dr. L. McLane Tiffany, of Baltimore, be made an Honorary Member."

Despite the Report of Council referred to for 1907, Volume XXI for 1908 shows no change in Article IV of the Constitution regarding the number of Honorary Members and there is no note in the minutes to indicate there was any discussion of the change. No additional Honorary Members have been added; however, the death of a second Honorary Member is recorded, Dr. Thaddeus A. Reamy, of Cincinnati. The memorial to him, in Volume XXII for 1909, includes the following unusual sentence, "In 1890 he joined the Southern Surgical and Gynecological Society and in 1902 was made, by request, an Honorary Member."

Volume XXIII for 1910 continues to list Dr. Thaddeus Reamy under the Honorary Members, indicating he is deceased, even though the other Honorary Member who had died was listed only once. This is more unusual in view of the fact that the memorial notice on Dr. Reamy had appeared in the previous Transactions.

The Report of Council given on December 15, 1910 includes the following: "5. That the following names are proposed for Honorary Membership: Sir Thomas Myles, of Dublin; Mr. Mayo Robson, of London; Mr. Arbuthnot Lane, of London; Mr. B.G.A. Moynihan, of Leeds; Mr. Robert Jones, of Liverpool; Mr. H.J. Stiles, of Edinburgh, Mr. Rutherford Morrison, of New-Castle-on-Tyne." (See comments on Vol. LIX, 1947.)

Despite this election of seven new members, the Constitution still reads that the number of Honorary Members "shall not exceed ten."

In an attempt to explain the election of the large number of British surgeons, it occurred to me that there might be some record in the Royal College of Surgeons of England which might explain a traveling group that participated in the meeting of the Southern Surgical Association and were elected to Honorary Fellowship as a token of the appreciation of the Members for their visit. Mr. I. F. Lyle, Librarian, the Royal College of Surgeons of England, responded to my inquiries with interesting information but, unfortunately, this does not provide the answer for which I was searching. However, his letter is of sufficient interest, that it seems worthy of recording.

> "I have done some checking and as far as I can discover this (the meeting in December, 1910) was not an official College visit. Two of the names on your list, Sir Thomas Myles and H.J. Stiles were not Fellows of this College, but of the Irish and Edinburgh Colleges respectively, and there is no evidence to support a visit of this nature in the official records. I have also consulted a number of biographical sources in the hope of finding some mention of a visit in 1910 but here again I have drawn a complete blank. I cannot find that Moynihan visited the United States between his 1903 and 1917 visits while Arbuthnot Lane attended an international congress there in 1911, but not in 1909 or 1910. If any evidence of a visit existed I find it hard to believe that various biographers would not have mentioned it, particularly as the party apparently consisted of so many eminent and fast rising surgeons.
>
> A surgical travelling club, as you suggested in your letter, might have been the reason for these men to have been together. However I can only find the existence of two in Britain at that time, that which was founded by Berkeley Moynihan in July 1909 and which became the Moynihan Chirurgical Club in 1929. His initial invitation was to provincial surgeons of whom, apart from Moynihan himself only three, Robert Jones, Stiles and Rutherford Morison appear on your list. Furthermore, the first foreign meeting of the club was known to have taken place in Paris in 1911. The other club, 'The Surgical Club' was founded in 1910 and the first members were London, as opposed provincial, surgeons.
>
> All this strengthens my opinion that the names you have given me were not present at the Nashville meeting in December 1910, in fact, I think it unlikely they were collectively even in the United States at the time. However, I may be able to offer a solution. In his book *The life of Sir Robert Jones,* London, 1934, Frederick Watson wrote: 'Sir Harold Stiles, in July 1910, writing from Edinburgh (to Jones), where the American surgeons had been on a visit, after giving an account of their doings, in which he himself had taken a busy part, concludes. . . .' I wonder whether it was a party of American surgeons who visited Britain in 1910 and upon their return, those who were members of the Southern Surgical Association decided to honour their hosts by making them honorary members. It is only a theory but it seems to fit the facts and certainly at that time there seems to have been more American surgeons visiting Britain than British surgeons visiting the United States."

The first item on the Report of Council for December 14, 1911 reads: "1. Dr. Ferdinand Herff, of San Antonio, Texas, one of the Founders of the Association, one of the most prominent and able surgeons of his native State, and now at the advanced age of 91, be transferred from the roster of the Fellows to Honorary Membership." The list of Honorary Members includes 15 people, even though Article IV of the Constitution still reads the number shall not exceed ten.

In Volume XXV, 1912, Article IV of the Constitution has been changed and Section 2 reads as follows: "The Honorary Member shall not exceed 25 in number and shall enjoy all the privileges of other Members, excepting to vote or hold office, but shall not be required to pay any fee."

An addition to the role of Honorary Members is recorded in Volume XXVII for 1914 where item 4 of the Report of the Council for December 17, 1914 reads: "that Dr. Joseph Taber Johnson and Dr. Nicholas Schilling be transferred to Honorary Membership." Both of these men were members of the Association before they were made Honorary Members, Dr. Schilling having been a Founder Member and Dr. Johnson having been elected in 1889 and having served as Vice-President in 1896 and as President in 1899.

Volume XXIX for 1916 includes some significant changes in the Constitution and By-Laws as proposed by the special committee appointed to review these items. "Members" became "Fellows" throughout, including the designation of Honorary Fellows. Report of Council for December 13, 1916 includes the following item 3:

> "Article IV—The Honorary Fellows of the Association shall not exceed 25 in number. They shall be nominated by the Council and elected by the Association. They will not be required to pay any dues and shall enjoy the privileges of other members except that of voting or holding office. This exception does not apply to Founders."
>
> "7. The Council further recommends that the 7 surviving Founders of the Association be transferred to the list of Honorary Fellows. They are: Dr. R. N. Cunningham, of Birmingham, Alabama; Dr. J. D. S. Davis, Birmingham, Alabama; Dr. J. A. Goggans, Alexander City, Alabama; Dr. George Ben Johnston, Richmond, Virginia; Dr. John W. Long, Greensboro, North Carolina; Dr. I. S. Stone, Washington, D.C.; Dr. Hugh M. Taylor, Richmond, Virginia."

The following sentence appears at the end of the Report of the Council: "The Report of the Council was considered, section by section, as read, and on several motions, duly seconded and carried, was adopted." This suggests that the earlier rule to hold things over for 1 year was disregarded and that all of these changes were accepted. However, the change does not appear in the Constitution at the beginning of this volume of the *Transactions.*

The *Transactions* do record the death of Dr. L. M. Tiffany, who became an Honorary Member in 1907, but the memorial for him does not appear until the next year and is not signed.

In this volume, there is for the first and only time a separate listing of "Honorary Members" including all those so named before this date, and on the next page a listing of the newly designated "Honorary Fellows." After this year, the two lists are merged into one.

The change in Article IV of the Constitution as included in the Report of Council for the previous year is now part of the Constitution in Volume XXX for 1917.

In this volume, the list of Honorary Fellows includes the 7 Founder Members as provided for in the previous year's decision, but includes additional names beyond that. In the discussion of the recommendations for a change in the Constitution, Dr. John Wesley Long suggested that it would be a mistake to prevent individuals from voting or holding office if they had been members of the Southern and were now promoted to Honorary Fellowship. The President suggested that the rule could be overcome by excepting not only Founders, but those who had been active as Members in the last 2 years. Dr. Long made such a motion, which was seconded, and this was voted and carried. Despite the long discussion that is recorded, I do not find this altered wording in the Constitution in the *Transactions* for at least the next 3 or 4 years.

The list of Honorary Fellows has been moved and now immediately preceeds the list of Fellows. Fellows are now listed both alphabetically and geographically. The geographic list has no place for overseas members and those Honorary Fellows who were active members are no longer listed in the geographic section. Dr. William M. Polk of New York is listed as an Honorary Member who died, but including him there are now 25 names listed as "Honorary Fellows."

The confusion about Honorary Fellows continues to be apparent. Volume XXXI for 1918 no longer lists Dr. Ferdinand Herff but there is no indication that he died and there is no memoir on him. Dr. William Polk, whose death was reported the previous year, is so listed again in the Report of Council for December 19, 1918, and there is a memorial to him at the end of the volume. The name of Dr. Hugh M. Taylor is now listed under Honorary Fellows as a Founder.

In 1919, Volume XXXII, there is for the first time a specific listing of Honorary Members who attended the meeting. In addition, the Report of Council on December 18, 1919, comments: "There have been 106 regular Fellows present, in addition, and with much delight, we note the presence of 5 Honorary, but very active Fellows. Viz: Drs. J. W. Long, Louis F. McMurtre, E. S. Lewis, John S. Davis, and Isaac S. Stone. . . ." There are other changes in the status of Honorary Fellows since there is a note under Honorary Fellows of the death of Drs. James A. Goggans, S. Pozzi of Paris, and Nicholas Schilling of Texas. At the end of the *Transactions,* there is a memorial for Dr. Goggans but nothing on either Drs. Pozzi or Schilling, nor are memorials for either of these found in the subsequent volumes.

Volume XXXIII for 1920 continues the listing of Honorary Fellows, takes note of the death of Dr. Russell M. Cunningham, a Founder, and Dr. Joseph Tabor Johnson, plus recording a new Honorary Fellow, Dr. Albert Vander Veer of Albany, New York, bringing the total to 22 Honorary Fellows. The Report of Council makes specific note of the death of Dr. J. A. Goggans, even though this had been recorded in the *Transactions* for the previous year.

The listing of two Honorary Fellows who attended the meeting is continued in Volume XXXIV for 1921. The overall listing of Honorary Fellows notes the death of Dr. Hugh M. Taylor of Richmond, Virginia but does not record two deaths that are mentioned in the Report of Council, that of Dr. R. M. Cunningham of Ensley, Alabama and Dr. Joseph Tabor Johnson of Cherrydale, Virginia. The *Transactions* for the previous year had indicated the death of these two individuals and there is a memoir in this volume for Dr. Johnson but not for the others.

With the establishment of the category of Senior Fellows, as recorded in Volume XXXV for 1922, there now appears between the lists of Honorary Fellows and regular Members, a separate listing of Senior Fellows. The list of Senior Fellows does not include the names of those who are Honorary Fellows nor does it list other Founder Members. Article IV of the Constitution now contains the same wording regarding Honorary Fellows but has a second paragraph dealing with Senior Fellows. The list of Honorary Fellows does not include Dr. R. B. Maury or Dr. Herman Tuholske, though the Report of Council indicates both of them had died as had Dr. Hugh M. Taylor and there are memorials to all three of these in this volume of the *Transactions.*

The death of Dr. Louis S. McMurtre of Louisville, Kentucky, is recorded in Volume XXXVII for 1924, which also includes a memorial to him.

Volume XXXIX for 1926 continues to list Dr. John Wesley Long under the category of Honorary Fellows. However, Report of Council records his death, there is a memorial to him in the volume, and he is still listed as both an Honorary Fellow and a Founder Member in Volume XL for 1927. The election to Honorary Fellowship of Dr. Rudolph Matas is recorded in Council Report for December 15, 1927.

The name of Dr. O. Morisani of Naples, Italy is dropped from Volume XLI for 1928 but his death is not recorded nor is there a memorial to him. Volume XLIII for 1930 handles Dr. A. Martin of Berlin in the same fashion and one can only assume that this is meant to record his death.

The death of Dr. John D. S. Davis of Birmingham, Alabama is recorded in Volume XLIV, 1931, in the Report of Council, but elsewhere he is listed as a Fellow with no indication of his status as an Honorary Fellow. There is a memorial to him which is the only signed memorial in this particular volume.

The name of Dr. Albert Vander Veer of Albany, New York, has been dropped from the list of Honorary Fellows but his death is not noted in the minutes for either 1930 or 1931 and there is no memorial to him in either of these years.

A new tradition, which seems to have been spontaneous, appeared following the Report of Council for December 10, 1931: "10. The distinguished guest, Dr. William J. Mayo, of Rochester, Minnesota, has been a guiding star and an inspiration to Southern surgeons be elected to Honorary Fellowship." At the close of that session, the President, Dr. Hugh Trout, asked Dr. William Mayo if he would like to make any comments as a newly elected Honorary Fellow. Dr. Mayo's comments cover 4 pages in the minutes, which he introduced as follows: "In looking over the names of the group of distinguished surgeons that have been chosen for Honorary Fellowship, I am reminded of pleasant associations with them, and I am fortunate, indeed, in having memories of all of them." Dr. Mayo was either the first or one of the first individuals who was present at the meeting where he was elected primarily as a Honorary Member without having been a member before that time. It was perhaps this combination of factors that lead to the tradition, which has persisted since, of asking Honorary Members to make some comment.

In 1932, Volume XLV breaks with tradition once again in indicating that two individuals were elected Honorary Members in 1931, Dr. William J. Mayo and Mrs. W. E. B. Davis of Birmingham, Alabama. Mrs. Davis is the only woman ever elected to Honorary Membership, the only non-M.D. ever to hold membership, and there is nothing in the minutes for either this year or the previous year to indicate the action taken electing Mrs. Davis to Honorary Fellowship. Her status as the widow of Dr. W. E. B. Davis would explain this action but it is strange that there is no record of the action in the *Transactions.* This same year, the name of Robert Jones of Liverpool has been deleted from the list of Honorary Members with no other indication of his death.

Honorary fellows are listed in alphabetical order in Volume XLVIII for 1935, previously having been listed chronologically by the date of election to Honorary Fellowship. The list indicates the death of Dr. Isaac S. Stone as the last of the Founder Members in the Honorary Fellowship category but does not include Dr. Ernest Lewis whose death is recorded in the Report of Council for December 12, 1935, along with his honorary fellowship status and for whom there is a signed memorial. It is interesting that the death of Dr. Stone is not mentioned in the Report of Council, until the following year, at which time there is also a signed memorial note on Dr. Stone.

Some interesting changes appear in Volume XLIX for 1936. Two Honorary Fellows are indicated as being present, Mrs. W. E. B. Davis, and this would appear to be her first meeting as an Honorary Fellow, and Dr. Rudolph Matas. Article 7 of the Council Report reads: "Dr. J.M.T. Finney be transferred from Senior Fellowship to Honorary Fellowship," and his name has been added to the list at the front of the volume as an Honorary Member.

The list of Honorary Fellows has deleted the names of Sir B. G. A. Moynihan and of George Foy. Lord Moynihan's death is also recorded in the Report of Council and there is a memorial to him signed by W. J. Mayo, the first such memorial to a foreign Honorary Member. There is no record that Lord Moynihan ever attended a meeting of the Southern Surgical Association and since this was during a period when Honorary Members attending the meeting were so indicated, it seems entirely possible that he never participated in any of the activities of the Association.

The death of Sir Thomas Myles is recorded in Volume L for 1937 and there is a signed memorial to him in the *Transactions,* with apparently all memoirs being signed by this time. The list of Honorary Fellows no longer includes Charles Jacobs although there is no other indication of his death and there is no memoir to him.

The death of Honorary Fellow Dr. W. J. Mayo is noted in Volume LII for 1939 in the Report of Council and there is a signed memorial to him. Another death recorded at the same time and also included in the list of memorials is that of Dr. C. H. Mayo. With the elimination of Dr. Mayo from the list of Honorary Fellows, the total list is now down to six.

The number of Honorary Fellows is further reduced in Volume LV, 1943, to four, with the deaths of Drs. J. M. T. Finney and Sir Arbuthnot Lane being noted in the Report of Council and with signed memorials to each.

In Volume LVII, 1945, a new Honorary Fellow is acknowledged following Report of the Council for December 6, 1945: "The fourth recommendation and the Report of the Council is very short but very important; it is that Dr. Alan O. Whipple of New York be elected to Honorary Membership in the Southern Surgical Association." Dr. Whipple, who was present, gave a short response to his election.

In Volume LVIII, 1946, there are for the first time guests from outside the United States: Dr. Jaime De la Guardia from Panama and Dr. Oscar Ivanissevich, from Argentina. Still, there is no record of any Honorary Fellows from overseas being present.

The list of Honorary Fellows for Volume LIX, 1947, includes only one foreign Member, Mr. Rutherford Morrison of Scotland, and his death is indicated in the Report of Council for December 1948. However, of greater interest are the Report of Council for December

11, 1947, where the death of Sir Harold J. Stiles is recorded, and the memoir of him at the end of the *Transactions* signed by Dr. Rudolph Matas. There is a footnote to this memoir, part of which is reproduced here because of its interest to the entire history of honorary members.

> "At a meeting of the Southern Surgical Association (at that time, The Southern Surgical and Gynecological Association), held at Nashville, Tenn., on December 14–17, 1910, the following eminent British Surgeons, who were visiting the United States at that time, were elected to Honorary Membership: Sir Thomas Myles, of Dublin; Mr. Mayo Robson, of London; Mr. (Sir) Arbuthnot Lane, of London; Mr. G.S.A. (Lord) Moynihan, of Leeds; Mr. (Sir) Robert Jones, of Liverpool; Rutherford Morrison, of New-Castle-on-Tyne; Mr. (Sir) Harold J. Stiles, of Edinburgh.
>
> In the course of the 38 years that have intervened since that memorable date, Mr. Harold Stiles (later, Sir Harold) remained the last survivor of that distinguished group until April 19, 1946, when he also passed from this sphere to join the silent majority."

I am unable to tell that any of these Honorary Fellows who were elected from overseas ever attended a meeting. With all now deceased, Sir Harold Stiles' death being recorded this year, and Mr. Rutherford Morrison's being recorded in the following year, it is a strange commentary that none of them had ever been present at a meeting of the Society that elected such a large number to Honorary Fellowship at one time.

In the *Transactions* for 1948, Volume LX, the list of Honorary Fellows includes four names, the newest being Dr. W. Edward Gallie of Ontario, Canada, who was present at the meeting and who made comments after his election. It was noted in introducing him that he was the first Canadian to be elected to Honorary Fellowship.

In the following year, 1949, Volume XLI, another Honorary Member was elected and was also present to make comments following his election. Dr. Evarts Graham of St. Louis, among his early statements, said, "This is the first meeting of this Association that I have attended, although I have read the Transactions and have been told by many of my friends who are Fellows what a wonderful organization it is."

In 1950, Mrs. W. E. B. Davis was the only Honorary Fellow present, and in 1951, Drs. Gallie and Graham were the only two Honorary Fellows at the meeting.

Volume LXV, 1953, no longer includes the name of Mrs. W. E. B. Davis as an Honorary Member, the Report of Council records her death as an Honorary Fellow, and part of the memoir to her reads as follows: "In 1931, Mrs. Davis was unanimously elected an Honorary Fellow of the Southern Surgical Association, the only woman ever to be awarded this distinction." With her death, there was eliminated from the list of Honorary Members all of the original or Founder Members or their representatives, marking a significant turn in the activities of the Association.

The list of Honorary members in Volume LXVIII, 1956, does not include Dr. Evarts A. Graham, and his name is not on the list of people read as having died in the year, but there is a memorial to him in the *Transactions.*

The election of Dr. Howard C. Nafziger, of San Francisco, California, is recorded in Volume LXIX, 1957, and the minutes of the first day of the meeting record the death of the two Honorary Fellows, Drs. Evarts A. Graham and Rudolph Matas, both of whose names have been deleted from the list of Honorary Fellows. It is interesting that this list includes the name of Dr. Nafziger, noting that he was elected in 1958, even though the meeting was in December 1957. This volume contains the signed memoir on Dr. Matas.

The death of Dr. W. Edward Gallie and a memoir to him are recorded in Volume LXXI, 1961.

The election to Honorary Fellowship of Dr. Lester R. Dragstedt, of Gainesville, Florida, is included in the Report of Council for December 8, 1960 in Volume LXXII, which also contains a signed memorial note to Dr. Nafziger.

As noted in *Alice in Wonderland* things get curiouser and curiouser. Volume LXXIII for 1961 lists only Dr. Whipple as an Honorary Fellow, even though Dr. Dragstedt's election was recorded in the previous year. The minutes of the first day of the meeting record the death of Dr. Nafziger, even though the memorial to him had appeared in the *Transactions* of the previous year. The name of Dr. Dragstedt does not appear as an Honorary Fellow until Volume LXXVIII for 1966—6 years after his election.

Dr. Harvey B. Stone of Baltimore was elected an Honorary Fellow following the Report of Council for December 12, 1963, as recorded in Volume LXXV. Dr. Stone is listed as a Fellow with all of his previous titles and is also listed as an Honorary Fellow. Dr. Dragstedt's name does not appear at all. Dr. Whipple is only listed as an Honorary Fellow. The listing of Dr. Stone among the Fellows is the first time that I have been able to find an Honorary Fellow listed along with the regular membership. This year, for the first time, there is a geographic list of members and a list of deceased members, with those who are Founder Members being identified by an "F" but there is no identification accorded to Honorary Members. Dr. Alan O. Whipple is recorded as a deceased Honorary Member and there is a memorial.

Volume LXXVI, for 1964, lists Dr. Harvey Stone as the only Honorary Fellow, which is the lowest number of Honorary Members recorded since they began to be listed separately. In reality this is an error, since Dr. Dragstedt should be listed.

Professor Phillip Sandblom of Lund, Sweden was elected to Honorary Fellowship on December 9, 1970, Volume LXXXII. This volume records three Honorary Fellows, the other two being Drs. Dragstedt and Stone. Neither Dr. Sandblom nor Dr. Dragstedt were listed anywhere among the Fellows but Dr. Stone continues to maintain his listing there, along with his listing as an Honorary Fellow.

In Volume LXXXIV, 1973, the three Honorary Fellows are listed as such and for the first time all three are also included in the full listing of the Fellows. All three are also in the geographic list of Fellows and are identified as Honorary Fellows. Furthermore, there is specific mention that Dr. and Mrs. Dragstedt and Professor and Mrs. Sandblom were all present at the meeting.

In December 1975, the death of Dr. Dragstedt is noted. In Volume LXXXIX, 1977, the death of Dr. Harvey B. Stone is recorded, with memoirs in this volume to both Drs. Dragstedt and Stone, Dr. Sandblom now being the only Honorary Fellow alive.

Dr. Sandblom, the only living Honorary Fellow, attended the meetings in 1978 and 1980.

In 1981, as recorded in Volume XCIII, the Report of Council suggested the Association was taking another rather new and different step in recommending that Honorary Fellowship be conferred posthumously on one of its Members. The explanation given in the meeting was that the nomination of Dr. Alton Ochsner as an Honorary Member had been suggested the year before while he was still alive, with the understanding that it be acted on at the meeting this year. In view of the fact that there had been a consensus to approve this before his death, the decision was made to complete this election. In the same volume is the signed memorial note for Dr. Ochsner.

Two major changes are noted in Volume XCIV for 1982. The election of Dr. John D. Martin, Jr. of Atlanta to Honorary Fellowship is recorded along with his comments following his election. Thus, for 2 years in a row, former Presidents and Members of long standing had been elected to Honorary Membership.

The other important change is that, for the first time, there is a complete listing of the Honorary Fellows. This appears just after the list of meeting places, dates, and presiding officers, and immediately preceeding the list of the Fellows. The Honorary Fellows are listed alphabetically with the date of their election. The only ones listed as being alive are Drs. Martin and Sandblom, both of whose names appear on the facing page above the list of Fellows, where they are listed as Honorary Fellows. Despite this significant change, there continue to be discrepencies in the overall listing of the Honorary Fellows. Dr. Sandblom is listed alphabetically and has his Honorary Fellowship indicated, whereas Dr. Martin's listing among the Fellows does not indicate his Honorary Fellowship. On the other hand, in the geographic listing, both of them have their Honorary Fellowship indicated.

The meetings for 1983 and 1984 were attended by both Drs. Martin and Sandblom, perhaps setting a new record with all the living Honorary Fellows attending these meetings.

In 1985, Volume XCVII, another former President was elected to Honorary Fellowship. In this case, the Honorary Fellow's contributions to the Southern Surgical Association and to surgery in general were pointed out to indicate the significant number of times he and his department had made direct contributions to the meetings of the Association. Dr. H. William Scott, Jr., of Nashville, Tennessee, followed the custom of making comments following his election.

Volume XCVIII for 1986 records another proposed change in the Constitution. An Ammendment was proposed for Article IV, Section I, as follows: "The Honorary Fellows of the Association shall not exceed twenty-five in number. They shall be nominated by the Council and elected by the Association. They will not be required to pay any dues and shall enjoy all the privileges of other Fellows except that of holding office." This change restored the vote to Honorary Fellows, but made no other changes. In accordance with custom, the proposal would be voted on at the next annual meeting and was passed in 1987.

During this meeting another Honorary Fellow was elected, Dr. Warren Cole of Asheville, North Carolina.

At the Centennial Meeting in 1987, another precedent was shattered when Dr. Robert S. Sparkman was elected to Honorary Fellowship at the beginning of the meeting rather than at the end as had been the custom for all previous elections of Regular and Honorary Fellows. This change was decided on at the Council meeting in the previous year, and was meant to recognize the tremendous effort of Dr. Sparkman in planning, organizing, and conducting the special activities of the Centennial Meeting. His comments were a clear indication of his emotions and his gratitude for this honor.

The concept of Honorary Fellowship in the Southern Surgical Association has undergone a number of changes from the original statement that there should be no Honorary Fellows, to a decision that there be a limit of 10 Honorary Fellows and that these come from foreign countries, to including not only Americans but members of the Association in the Honorary category and then increasing the number to 25. In 1912, the restriction to foreign members was formally removed from the Constitution and has not been a matter of concern since then. The exact explanation for the election of a number of foreign members to Honorary status in the relatively early days of the Association is not explained and this policy was essentially discontinued until recently when a new foreign Honorary Fellow was added to the list.

A change in 1916 converted all of the surviving Founders to the list of Honorary Fellows, there being only seven survivors at that time, and each of these continued in the Honorary category until his death. In 1931, another significant change occurred with the election of the only woman as an Honorary Fellow and the only non-M.D. to have ever been accorded Fellowship as well as the only woman to have ever been a member of the Southern in any category.

In the 1940s, there were relatively few Honorary Fellows listed and by the 1960s the number had dropped to an all time low of 1 or 2. From 1975 to 1982, there was only one Honorary Fellow alive, although another precedent was broken during this period when a former Member was elected posthumously to Honorary Fellowship.

The 1980s have seen an increasing interest in the election of individuals to Honorary Fellowship, and all of the recent nominees have been long-standing members of the Southern.

Because precedents have been broken repeatedly in the past, it seems likely that the future history of the Southern Surgical Association will see additional changes in this category and everyone with an interest in the Southern Surgical Association will watch these developments with keen anticipation.

Southern Surgical Association

The Ninety-Seven Presidential Addresses 1888–1987

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A LIST OF THE PRESIDENTS of the Southern Surgical Association and the titles of their presidential addresses for the first 100 years of its existence are found in the Appendix. A number of the early addresses were not given titles. These are identified and a one-line description of the subject has been added. Beginning with President Haggard's address in 1888 and through Sawyers' memorable contribution in 1987, there have been 97 published addresses. The three "missing" addresses are explained as follows. In 1904, Floyd McRae was ill and no presidential address was given or published. In 1923, the presidential address by James Mitchell was a slide-illustrated travelogue that was not published. In 1942, the Southern Surgical Association did not meet because of the war. Barney Brooks was President in 1942 and 1943 and gave the presidential address in 1943. There were two other deviations from custom. In 1953, President Bigger was ill and the presidential address was not delivered at the meeting but was published in the *Transactions.* In 1961, President Joseph Donald died before the annual meeting. In accordance with Article VI, Section 2 of the Constitution, Vice President William H. Prioleau of Charleston presided as the President Pro Tem and delivered the presidential address.

With the exceptions just described, the presidential addresses have been delivered at the annual meeting and published in the *Transactions*. Publication in the *Annals of Surgery* was begun in 1936.* The addresses have been given at different points in the program, and the custom of delivering the presidential address at the first morning session of the annual meeting was established in the 1960s. The published addresses have varied greatly in length and should represent what was actually delivered. The presidential address has been an important part of the annual meeting from the beginning and wives have always been encouraged to be in attendance at its delivery. The fact that wives do attend in large numbers continues to be a charming and unique feature of the "Southern Surgical."

Time, space, and reader interest prohibit comments on each of the 97 addresses. Arbitrarily, the addresses are discussed in 20-year segments, selecting several from each segment for individual discussion. The criteria for selection are entirely the author's and will not please every reader. Almost without exception, the addresses reflect careful thought and significant effort. To attempt to furnish an overview, the addresses have been assigned to five subject categories and this is presented in Table 1. Because many of the addresses touch on more than one category, the assignment is arguable. A final caveat is that the addresses have been judged on the basis of their significance by today's standards and it is likely that this assessment would have been different at the time the address was delivered.

1888–1907

The first presidential address by W. D. Haggard, Professor of Obstetrics and Diseases of Women, Medical Department, University of Tennessee, Nashville, was relatively brief. President Haggard began by commenting on the importance of the work of J. Marion Sims and made the interesting statement that had Sims not died, he (Sims) might be delivering the address. Dr.

Presented at the 100th Anniversary Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 6–9, 1987.

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* Publication of the *Transactions* and of the scientific papers in other journals is discussed elsewhere in this volume.

TABLE 1.

	1888–1907	1908–27	1928–47	1948–67	1968–87
Scientific	9	9	3	1	2
Historical	3	6	9	4	8
Ethic/Philos	4	3	3	9	3
Education	1	0	3	5	6
Miscellaneous	2	1	1	1	1

Haggard elaborated on the hopes for the future of the new organization. Interest in and regard for history and affection for the organization have continued to be hallmarks of the Southern Surgical Association.

The second president, Hunter McGuire of Richmond, was one of the best known surgeons of his time and his acceptance of the presidency was a major factor in the early success of the Southern Surgical and Gynecological Association. His untitled address filled 12 printed pages and began with a defense of the necessity for forming the organization. After admitting that the South lagged behind the North in scientific medical progress, President McGuire eulogized people of the South, including a touching tribute to Confederate surgeons. He concluded with a ringing challenge to the members to continue the high standards and productivity of the traditional southerner.

The third president, George J. Engelmann of St. Louis, Missouri, was elected to membership in the Southern Surgical and Gynecological Association in 1889 and at the same meeting was elected President. His 29-page address (with no illustrations) was entitled "The Health of the American Girl, As Imperilled by the Social Conditions of the Day." The text is an incredibly obtuse argument that women are emotionally different, particularly during adolescence, and its condescending tone would certainly inflame the feminists of the present time. A typical statement (obviously not a sentence) deserves quotation: "The constriction and compression of the corset, the dragging pounds of the skirt, the circulation-impeding garter, the insufficiencies of low-necked dresses, of filmy stockings and thin shoes, and the total absence of protection where it is most needed, the absence of drawers."

The sixth presidential address was delivered at the New Orleans meeting in November 1892, by Bedford Brown of Alexandria, Virginia. Entitled "The Southern Surgical and Gynecological Association—Its Origin, Objects, and Aims," it was a valuable review of the founding, purposes, and early years of the Association. It included a tribute to J. Marion Sims and a clear statement that the organization never intended to be purely sectional but from the start was a national organization. In flowery language, Brown expressed pride in the recovery of the South and the progress of the new organization of surgeons and gynecologists.

George Ben Johnston of Richmond was the tenth president (1897). Johnston announced the subject of his untitled address in the second paragraph as "the prevalence of specialism and who shall be specialists." He further stated "The science of medicine has grown to such gigantic proportions that no one mind can any longer thoroughly master every detail of it; hence the necessity for specialism." While recognizing the desirability of the trained and experienced specialist, Johnston warned against "pseudospecialists" established by false credentials. He called upon the profession to recognize legitimate specialists and to educate the public in this regard. Johnston was a leading surgeon in Richmond and was the subject of the 1947 presidential address.

In 1901, President Manning Simons of Charleston, South Carolina, began his untitled address by noting the deaths during the preceding year of W. D. Haggard and Hunter McGuire, the first and second presidents of the Southern Surgical and Gynecological Association. Simons then stated that the subject of his address was an examination of whether the Southern Surgical and Gynecological Association justified its existence during its first 14 years. Simons concluded that the organization had done so and further suggested an examination similar to that for licensure of individuals who wished to practice specialties, particularly surgery and gynecology.

In 1902, the president was W. E. B. Davis of Birmingham, the single individual most responsible for the founding of the Southern Surgical and Gynecological Association. He was elected secretary at the first meeting and served for 13 years in that capacity. Appropriately, Davis's address, although not given a formal title, dealt with the founding and early years of the organization. His account was more specific and less concerned with attitudes than that of Bedford Brown in 1893. Davis made a number of suggestions regarding the organization that apparently were accepted. The most unusual of these was the suggestion that a sketch of the life of Robert Batty be included in the next volume of the *Transactions*. Batty was a gynecologist from Rome, Georgia, who popularized transvaginal removal of normal ovaries for a variety of complaints. He was not a member of the Southern Surgical and Gynecological Association. Davis was killed in a train-carriage accident shortly after the meeting, and the following year one of the projects he had suggested for the organization was altered to become a tribute to him.

President Howard A. Kelly's address in 1907 was entitled "Art Applied to Medicine and Surgery." This was a scholarly description of the development of medical illustration profusely illustrated by examples of the works being discussed.

1908–1927

In 1911, Rudolph Matas' presidential address was entitled "The Cinematograph as an Aid to Medical Education and Research" with a subtitle "A Lecture Illustrated by Moving Pictures of Ultramicroscopic Life in the Blood and Tissues, and of Surgical Operations." In this long, detailed presentation, Matas described several aspects of the development of motion picture technology including a brief history of the entertainment motion picture industry that was then in an early stage of development. More time was spent in discussing the scientific applications of the techniques. Matas' predictions of future uses were amazingly accurate. At the time, Matas was probably the leading surgeon from the "deep" South and his active participation in and affection for the Southern Surgical and Gynecological Association were important to the organization.

The following year, another internationally known surgical leader, J. M. T. Finney of Baltimore, entitled his presidential address "Surgical Judgment." Finney, educated at Princeton and Harvard, was William Stewart Halsted's "right hand" at Hopkins. He was a highly respected surgeon and a much loved individual. To the current reviewer, the wording of the address seems tortuous. An early paragraph is an illustration—"This is a difficult task which we have set ourselves, because it will be at once apparent that judgment and experience are very closely associated and interdependent, the one upon the other, and that in the consideration of each one separately, and in their several relations, one with the other, there are many different factors to be borne in mind, the relative measure of importance of which it will be found impossible accurately to determine." Finney delivered a strong indictment of American medical education at the time and cited the recently released Flexner Report. He called for public education regarding selection of surgeons and for restricting the performance of operations to those trained as surgeons. Finney's son was to be president in 1959 and, except for a tragic early death, a grandson would have been a strong candidate for the office.

The 1916 address of Thomas S. Cullen, entitled "America's Place in the Surgery of the World," is 35 pages in length with no illustrations and no bibliography. Cullen, a distinguished gynecologist at the Johns Hopkins Hospital and successor to Kelly, covered many aspects of the development of surgery in the United States and summarized its current status. Cullen made the interesting comment "I have seen another surgeon of excellent repute place the handle of his knife in his mouth for safe-keeping while he was busy tying ligatures." In another section of the address, Cullen gave the following advice to surgeons "If you wish to do your maximal amount of good work, you must take at least a two months' vacation each year." This did not include time spent at surgical meetings, which he also recommended.

In 1917, the president of the Southern Surgical Association was William D. Haggard of Nashville. Haggard, son of the first president of the "Southern," was secretary for 16 years beginning in 1901, and his election as president for the year following his term as secretary established a precedent that has not been broken. The title of his address was "The Medical Profession and the Great War." President Haggard lauded the ideals of the Allies—"Our loftiest aims and most sacred ideals have been crystallized and formulated by that great seer, that incomparable patriot and immortal statesman, Woodrow Wilson, Prime Minister of the world." He pointed out that the first American officer to be killed was a physician, Lieutenant Fitzpatrick of the Washington University-based hospital unit, and paid tribute to the Army Medical Corps for its achievements in public sanitation and to William C. Gorgas for his role in the Panama Canal and for his organization of the medical corps for the war. Haggard even cited benefit from the war as follows: "Already this war has emancipated men from the slavery of alcohol, the greatest curse and blight upon humanity."* He also noted great progress in the surgical management of wounds and closed by quoting a poem of Oliver Wendell Holmes, the last stanza of which follows: "Along its front no sabers shine, No blood-red pennons wave, Its banner bears the single line —Our glory is to save."

"Some Tendencies in Contemporary Medicine of Special Interest to Surgeons" was presented by C. Jeff Miller of New Orleans, president in 1922. Miller discussed the state of medical practice and medical organization in the United States and expressed reservations about the burgeoning interest in laboratory medicine. "Sir James McKenzie warned against this when he very correctly said that a hundred new methods of investigating disease in the living increased by just that number the chances for going astray." He mentioned that "socialized medicine is being widely discussed," the first time that phrase appears in a Southern Surgical presidential address.

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* When this was presented at the Centennial, it was suggested that many present at the meeting seemed pleased that the emancipation was incomplete.

In 1924, LeGrand Guerry of Columbia, South Carolina, delivered the presidential address entitled "Luke, the Greek Physician and Historian." This is one of the most interesting of the presidential addresses. Beginning with a detailed account of what was known of Luke and his life, Guerry traced his accomplishments in chronicling the events of his time. Guerry then shifted to a call for increased religious commitment beginning by stating "Woodrow Wilson, in one of his clearest moments said: 'The sum of the whole matter is this, that our civilization cannot survive materially unless it be redeemed spiritually'."

1928–1947

"No apology needs to be made upon an occasion such as this because of the selection for discussion of a disease which is the most dreaded, most misunderstood, most mismanaged and most mistreated of any disease with which the medical profession has to deal." So began the 1928 presidential address by A. C. Scott of Temple, Texas, entitled "Consistency in the Surgical Treatment of Cancer." After brief comments on the ancient recognition of cancer, Scott put forward clinical observations suggesting that the cause of cancer is a parasite. He recognized that such was not the prevailing opinion of leading pathologists. He further cited evidence that trauma plays a role in the etiology of cancer and that the development of cancer is influenced by immune responses. He presented a realistic but conservative view of the place of surgery in the treatment of cancer and dwelled on the hazards of mechanically spreading cancer cells in operative wounds. He favored the use of the hot cautery in cancer operations. The technique was demonstrated by a motion picture.

President Hugh H. Trout of Roanoke, Virginia, delivered the 1931 address entitled "An Appraisal of the Surgical Treatment of Pulmonary Tuberculosis." The paper is an interesting account of the treatment of pulmonary tuberculosis before any form of chemotherapy, but it is cited because of the bibliography covering only the period 1925 through 1932 and consisting of 1224 published articles! There was even an index of the bibliography. In the text, Trout cited sources of bibliography of the same subject before 1925.

Harvey B. Stone of Baltimore, President in 1936, addressed "Wider Horizons for the Surgeon." This is a well-written discussion of the effects of progress in the physical sciences on such important topics to the surgeon as the cause of cancer. Stone issued a plea that surgeons expand their interests to broader areas in search of relevant new information.

For the fiftieth year of its existence, the Southern Surgical Association met in Birmingham and President Fred W. Rankin's address was entitled "Milestones on the Road of Surgery." After a brief account of the founding and early years of the Southern Surgical Association, Rankin reviewed the important events leading to the development of surgery as a discipline. The subjects ranged from the development of anatomy through the founding of surgical organizations including the American Board of Surgery.

On December 9, 1941, at Pinehurst, North Carolina, Harry Hyland Kerr delivered the presidential address entitled "Once Again." Kerr expressed the opinion that the failure of the United States to join the League of Nations and to provide leadership after World War I were major factors in allowing the rise of militant fascism. Delivered 2 days after the Japanese attack on Pearl Harbor, the text did not mention Japan and identified only Germany as the enemy. The address was obviously prepared when war was imminent and at least the written text was not altered after the attack. Kerr's comments on the magnitude of the neuropsychiatric problems of a drafted army were clearly and unfortunately not heeded.

At the Pinehurst meeting, Barney Brooks, chairman of the Department of Surgery at Vanderbilt University School of Medicine, was elected president. Because of wartime restrictions on travel, no meeting of the Southern Surgical Association was held in 1942, and Brooks became the first and, so far, only individual to be president of the Southern Surgical Association for 2 years. Although the war continued, the 1943 meeting of the Southern Surgical Association was held in New Orleans, and Brooks' presidential address was entitled "Psychosomatic Surgery." Brooks began by commenting that surgery had progressed from anatomic and pathologic emphasis to physiologic emphasis. He used the term "materialistic philosophy" repeatedly and the meaning of this is not clear to the author. He then turned to a consideration of psychiatry and gave his beliefs about the place of psychiatry and its relationship with the field of surgery. He described but did not completely report the results of an ongoing experience of having psychiatrists interview all surgical patients.

In 1944, the Association met in Hot Springs and it seems remarkable that anyone got to the meeting. President Alton Ochsner's address was entitled "Whither Anon" Ochsner pointed out that medical education and particularly postgraduate education had suffered badly during the war and that provisions would be necessary for expanding residencies in the immediate postwar period. Ochsner then considered the future of the practice of medicine. He marshalled evidence that a substantial proportion of the population of the United States did not have access to adequate medical care and that because of readily explainable rising costs, this problem was likely to increase in magnitude. He further suggested that the profession take the lead in fostering some form of national plan for making health care available to all.

Perhaps the most quoted presidential address was that given in 1946 by Daniel C. Elkin of Atlanta. Entitled "The Georgia Blister and Critic," the paper is an account of the activities of H. A. Ramsey, an apparently self-styled physician, whose qualifications included little, if any, education. Beginning in 1854, Ramsey published a monthly journal entitled *The Georgia Blister and Critic.* This consisted principally of scurrilous attacks on the many objects of Ramsey's dislike. Ramsey practiced medicine and campaigned for a faculty position in the new Atlanta Medical School, which was not forthcoming. The final paragraph described Ramsey's arrest on charges of fraud and stated that he absconded and had not been heard of since. In the writer's opinion, it is the most curious of the presidential addresses and one wonders if there was some meaning that time has obscured.*

1948–1967

President Edwin Lehman's address in 1948 was entitled "The Surgical Man." It is a brief, thoughtful, and pleasant discussion of the facets of surgery that attract surgeons and of the facets of personality required by and nurtured in surgeons.

In 1949, the presidential address, entitled "Problems in the Training of the Surgeon," was given by Alfred Blalock, incomparable chairman of the Department of Surgery at the Johns Hopkins University School of Medicine. The address began with reference to a presentation by William Stewart Halsted at Yale University in 1904 describing the residency program at Hopkins. Blalock went on to cite the success of the Halsted system of educating surgeons and then to discuss the threats imposed by the rising cost of medical care and increasingly available health care insurance. Addressing as it did one of Blalock's most intense interests, the paper is a good example of his extraordinary vision.

Deryl Hart of Duke University gave the 1956 presidential address entitled "The Responsibility of the Medical Profession to Medical Education" with the subheading "Contributions of the Geographic Full Time Staff to the Development of the Duke University School of Medicine and Suggestions for the Assumption of More of the Cost of Medical Education by the Medical Profession as a Whole." Hart outlined the development of a unique relationship between the administration of Duke University and the medical faculty. It seems likely that the spirit of harmony, fairness, and justice described in this address was a factor in the emergence of Duke as one of the leading medical institutions of this country.

The shortest printed presidential address of our first century was that of Floyd W. McRae of Atlanta, Georgia, given in 1957 and entitled "As It Was In the Beginning." McRae's father was President in 1904 and did not give the presidential address because of illness.

James D. Rives of New Orleans, President of the Southern Surgical Association in 1958, gave an address entitled "The Impact of the American Board of Surgery Upon Surgical Education in the United States." After briefly reviewing the founding of the American Board of Surgery, Rives gave some perceptive comments about its function and its effects on surgical education. Rives concluded that the American Board of Surgery had become an exceedingly powerful voice in surgical education and that it had, in general, satisfied its aims of elevating the standards of the practice of surgery.

"What the Southern Surgical Association Means to Me" was the title of the 1960 presidential address by Francis M. Massie. Saying "If the conclusion of this address sounds to you flowery and romantic, it is because I am flowery and romantic," Massie, with humor and grace, expressed the affection for the "Southern Surgical" shared by so many members for now 100 years.

In 1962, Robert M. Moore of Philadelphia was President and his address was entitled "The Davis Brothers of Birmingham and the Southern Surgical and Gynecological Association." This is the most complete and concise account of the founding of the Association and its early years before Sawyers' and surely will be referred to many times at the Centennial Celebration. Moore was chairman of the Department of Surgery at the University of Texas Medical Branch in Galveston and became Secretary of the American Board of Surgery.

On the 75th anniversary of the Association, President James A. Kirtley, Jr. of Nashville presented "A Panorama on the Seventy-Fifth Anniversary of the Southern Surgical Association." Kirtley reviewed highlights of the first 75 years including comments on some of the early presidential addresses.

Now an Honorary Member, J. D. Martin's presidential address in 1964 was entitled "The Crossroads of Surgery." Martin traced the changes in the discipline of surgery occurring during the existence of the Southern Surgical Association. He expressed the opinion that increasing government intervention had brought surgery to a crossroads and suggested appropriate directions to consider.

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* In 1987, the author asked Doctors W. Cole, Laman Gray, Sr., W. Hamm, J. D. Martin, Ed Parker, R. S. Sparkman, and G. Yeager, most of whom heard the 1946 address, to comment on any "hidden meaning." All agreed there was none.

1968–1987

The presidential addresses of the last 20 years were heard at their original presentation by many who will be present at the Centennial. Given, as was true earlier as well, by men who contributed much to the Southern Surgical Association and to American surgery, they are of high quality and continued interest. There is no truly rational way to select some for comment and to appear to ignore others.

In 1971, Edward F. Parker's presidential address was entitled "Metamorphosis in Medicine—For Better or For Worse." This was an examination of some of the problems facing medicine and the changes being considered. Parker questioned the reliability of the data on which a physician shortage was predicted. His discussion of the financing of health care is pertinent today.

In 1973, President James Hardy's presidential address was entitled "She is Risen" and was a provocative discussion of the role of the Southern Surgical Association and its place in the rise of the South.

The 1974 presidential address of David C. Sabiston, Jr. was entitled "Major Contributions to Surgery from the South" and was a characteristically well-composed account of the achievements of McDowell and others up to Blalock. Among the illustrations were several prepared specifically for the address by Mr. Leon Schlossberg. Sabiston acknowledged these as follows: "In these beautiful half-tone illustrations, this distinguished medical artist has made a unique contribution to medical history."

In 1975, President William H. Muller, Jr. traced the development of scientific and specifically surgical societies. This address should be required reading for all surgical residents.

Walter Becker's account of the development of thyroid surgery in 1976 will become a classic reference.

In 1977, H. William Scott, Jr. skillfully drew an analogy between a prerevolutionary armed dispute in North Carolina and the increasing tide of federal regulations affecting surgery in particular.

Robert S. Sparkman, president in 1978, presented a carefully researched and fascinating account of Jane Todd Crawford, the patient of Ephraim McDowell who underwent the first ovariectomy in 1809.

A former secretary and, in 1979, President of the Association, W. Dean Warren discussed the steps in the development of portosystemic shunting. Representing the views of the leading authority on the subject, the paper is of unusual interest.

A detailed history of surgery and surgeons of North Carolina was given by President Felda Hightower in 1980 and certainly qualifies Hightower as a griot.*

Long-respected Laman Gray, president in 1981, discussed the development of the residency program in Gynecology at Hopkins and made recommendations for improved education of those interested in pelvic surgery.

The presidential address in 1982, delivered by the author of this chapter, was a historical review of appendicitis.

Isidore Cohn, Jr., president in 1983, gave a candid and poignant discussion of the challenges and dilemmas faced by chairmen of departments of surgery.

In 1984, President George L. Jordan traced the evolution of medical care from the "unicellular" stage, through many false starts, to the current complex system.

The 1985 presidential address by Robert Zeppa was a timely and sobering look at the cost of graduate medical education and the upcoming problems in providing the necessary funding.

In 1986, President Arlie R. Mansberger, Jr. began with a quote from T. S. Eliot, proceeded to discuss the external forces affecting medical care, and made suggestions for altering medical education to prepare physicians more adequately for the times.

At the Centennial meeting, John Sawyers (from Nashville, as was the first president) reviewed the early history of the organization in a scholarly, comprehensive, and entertaining account entitled "The Origin and Early Development of the Southern Surgical Association."

The presidential addresses of the first 100 years of the Association are, individually and collectively, tributes by its elected leaders to the wonderful organization now known as the Southern Surgical Association. It is hoped that these addresses will continue to be sources of pleasure and stimulation to the membership in the decades and even centuries to come.

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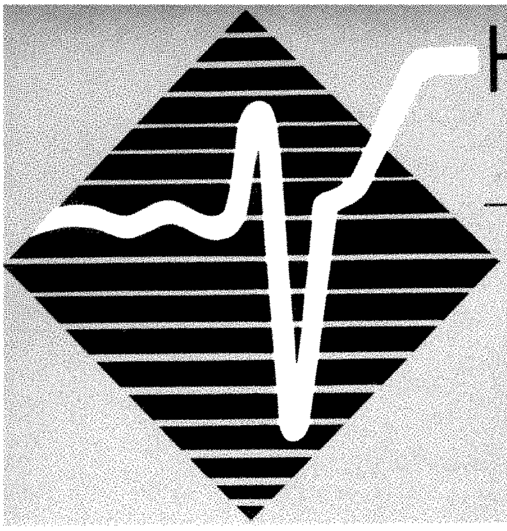
* A word used by Hightower connoting leadership. It is not included in Webster's Unabridged Dictionary but has been located by computer search of several data bases. Usually it refers to African tribal storytellers or bards.

Appendix
Presidents of the Southern Surgical Association 1888–1987

Year	President	Title of Presidential Address
1888	W. D. Haggard	Untitled—A tribute to Sims and welcome to the members of the new organization.
1889	H. H. McGuire	Untitled—Defends the need for the new organization.
1890	G. J. Englemann	"The Health of the American Girl, As Imperilled by the Social Conditions of the Day"
1891	L. S. McMurtry	"A Plea for Progressive Surgery"
1892	J. McF. Gaston	"Compatibility of Conservative and Aggressive Surgery"
1893	B. Brown	"The Southern Surgical and Gynecological Association—Its Origin, Objects, and Aims"
1894	C. Kollock	Untitled—A brief (five page) review of the contributions of Southern surgeons and gynecologists with emphasis on McDowell.
1895	L. McL. Tiffany	Untitled—An oblique discussion of the duties of physicians to make accurate observations and to share these with others.
1896	E. S. Lewis	Untitled—A discussion of then-current controversies in pelvic surgery.
1897	G. B. Johnston	Untitled—Subject stated in the second paragraph—"the prevalence of specialism and who shall be specialists."
1898	R. Douglas	"Acute General Peritonitis"
1899	J. T. Johnson	Untitled—An overview of the current status of surgery and gynecology.
1900	A. M. Cartledge	"A Plea for the Better Appreciation of the Limitations of our Operative Work"
1901	M. Simons	Untitled—A look at the achievements of Southern medicine and the Southern Surgical and Gynecological Association.
1902	W. E. B. Davis	Untitled—A review of the history of the Southern Surgical and Gynecological Association.
1903	J. W. Bovee	"The Progress of Ureteral Surgery"
1904	F. W. McRae	No address given due to illness of the President.
1905	L. C. Bosher	Untitled—Comments on preparation for a career in surgery.
1906	G. H. Noble	"Surgical Treatment of Puerperal Thrombosis of Pelvic Veins"
1907	H. A. Kelly	"Art Applied to Medicine and Surgery"
1908	F. W. Parham	"Conservative Surgery, Then and Now"
1909	S. McGuire	"Latent and Active Neurasthenia in Its Relation to Surgery"
1910	W. O. Roberts	"Southern Surgeons and Surgery—Before, During, and After the Civil War"
1911	R. Matas	"The Cinematograph as an Aid to Medical Education and Research"
1912	J. M. T. Finney	"Surgical Judgment"
1913	J. Y. Brown	"Diagnosis and Surgical Technique to be Employed in the Handling of Acute Abdominal Conditions"
1914	J. W. Long	"The Wisdom of the Past, A Prophecy of the Future"
1915	B. Saunders	"The Great Professional Problem of the Present Decade"
1916	T. S. Cullen	"America's Place in the Surgery of the World"
1917	W. D. Haggard	"The Medical Profession and the Great War"
1918	I. S. Stone	"The Standardization of Rural Hospitals"
1919	J. E. Thompson	"Surgery and Embryology"
1920	W. Bartlett	"An Estimate of the Value of Local Anesthesia in the Surgery of Today"
1921	R. Winslow	"Retrospect and Prospect"
1922	C. J. Miller	"Some Tendencies in Contemporary Medicine of Special Interest to Surgeons"
1923	J. F. Mitchell	"A Surgical Travelogue" (Slides and moving pictures) Not published.
1924	LeG. Guerry	"Luke, the Greek Physician and Historian"
1925	I. Abell	"A Retrospect of Surgery in Kentucky"
1926	H. A. Royster	"The Influence of Tradition in Surgery"
1927	G. L. Hunner	"Calculus of the Upper Urinary Tract Treated by New Methods; End-Results"
1928	A. C. Scott	"Consistency in the Surgical Treatment of Cancer"
1929	L. E. Burch	"The Surgeon in the Making"
1930	J. M. Mason	"Early Medical Education in the Far South"
1931	H. H. Trout	"An Appraisal of the Surgical Treatment of Pulmonary Tuberculosis"
1932	R. S. Cathcart	"Surgery and Its Relation to Society"
1933	V. P. Blair	"Ruminations of a Journeyman Surgeon"
1934	F. K. Boland	"Progress in Surgery"
1935	R. L. Payne	"The Master Surgeon and the Layman"
1936	H. B. Stone	"Wider Horizons for the Surgeon"
1937	F. W. Rankin	"Milestones on the Road of Surgery"
1938	L. Noland	"The Panama Adventure"
1939	A. O. Singleton	"The Surgeon in the Romantic Story of Texas"
1940	J. S. Davis	"The Story of Plastic Surgery"
1941	H. H. Kerr	"Once Again"
1942	B. Brooks	No meeting because of World War II.
1943	B. Brooks	"Psychosomatic Surgery"
1944	A. Ochsner	"Whither Anon"
1945	C. A. Vance	"The Transylvania Medical Library"
1946	D. C. Elkin	"The Georgia Blister and Critic"
1947	F. S. Johns	". . . He Shall Have a Noble Memory"
1948	e. P. Lehman	"The Surgical Man"
1949	A. Blalock	"Problems in the Training of the Surgeon"

Appendix (*Continued*)

Year	President	Title of Presidential Address
1950	G. V. Brindley	"Surgery Forty Years Ago, Today and Tomorrow"
1951	F. C. Wilson	"Dr. Finney"
1952	I. M. Gage	"Thrombo-Embolic Phenomenon—A Local Process with Regional Spread and Systemic Complications"
1953	I. A. Bigger	"The Education of Surgeons"
1954	J. C. Burch	"What's Wrong with Pelvic Surgery?"
1955	C. Williams	"The Art of Surgery"
1956	D. Hart	"The Responsibility of the Medical Profession to Medical Education"
1957	F. W. McRae	"As It Was In the Beginning"
1958	J. D. Rives	"The Impact of the American Board of Surgery upon Surgical Education in the United States"
1959	G. G. Finney	"Publicity, the Public and the Medical Profession"
1960	F. M. Massie	"What the Southern Surgical Association Means to Me"
1961	J. M. Donald W. H. Prioleau	"Medical School Relationship to its Community: The Case for the Community Hospital"
1962	R. M. Moore	"The Davis Brothers of Birmingham and the Southern Surgical and Gynecological Association"
1963	J. A. Kirtley, Jr.	"A Panorama on the Seventy-Fifth Anniversary of the Southern Surgical Association"
1964	J. D. Martin, Jr.	"The Crossroads of Surgery"
1965	G. W. Horsley	Untitled—A call for re-emphasis on medical ethics.
1966	H. Mahorner	"Impressions"
1967	R. J. Coffey	"The Tempo of Change"
1968	R. J. Noer	"And Gladly Teach"
1969	G. H. Yeager	"Medical Schools of the Southern United States 1779–1830"
1970	H. Wilson	"The Contribution of Surgeons to Basic Science: Implications for Medical Education"
1971	E. F. Parker	"Metamorphosis in Medicine—For Better or for Worse"
1972	G. V. Brindley, Jr.	"The Changing Panorama of Medical Education"
1973	J. D. Hardy	"She is Risen"
1974	D. C. Sabiston, Jr.	"Major Contributions to Surgery from the South"
1975	W. H. Muller, Jr.	"Societies, Surgeons and Surgery"
1976	W. F. Becker	"Pioneers in Thyroid Surgery"
1977	H. W. Scott, Jr.	"The War of Regulation (1767–1977)"
1978	R. S. Sparkman	"The Woman in the Case. Jane Todd Crawford, 1763–1842"
1979	W. D. Warren	"Reflections on the Early Development of Portacaval Shunts"
1980	F. Hightower	"Surgeons of Early North Carolina"
1981	L. A. Gray, Sr.	"Training in Pelvic Surgery. With a Review of the Hopkins Method and Contemporary Opinion"
1982	G. R. Williams	"A History of Appendicitis. With Anecdotes Illustrating Its Importance"
1983	I. Cohn, Jr.	"Mr. Hunter Builds His Dream Department"
1984	G. L. Jordan, Jr.	"The Impact of Specialization on Health Care"
1985	R. Zeppa	"Graduate Medical Education. A Costly Continuum"
1986	A. R. Mansberger, Jr.	"Still Point. (Of the Turning World)"
1987	J. L. Sawyers	"The Origin and Early Development of the Southern Surgical Association"



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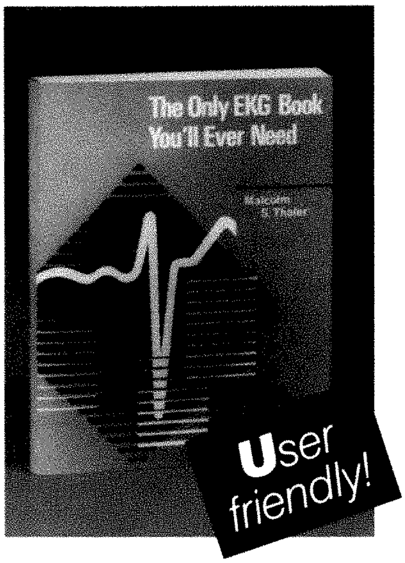

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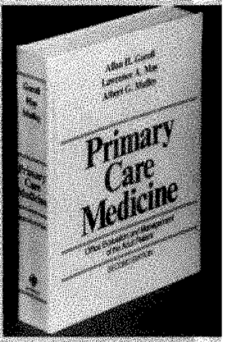

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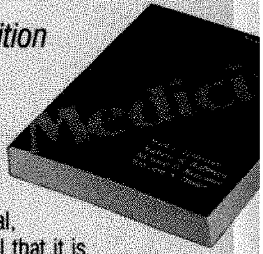

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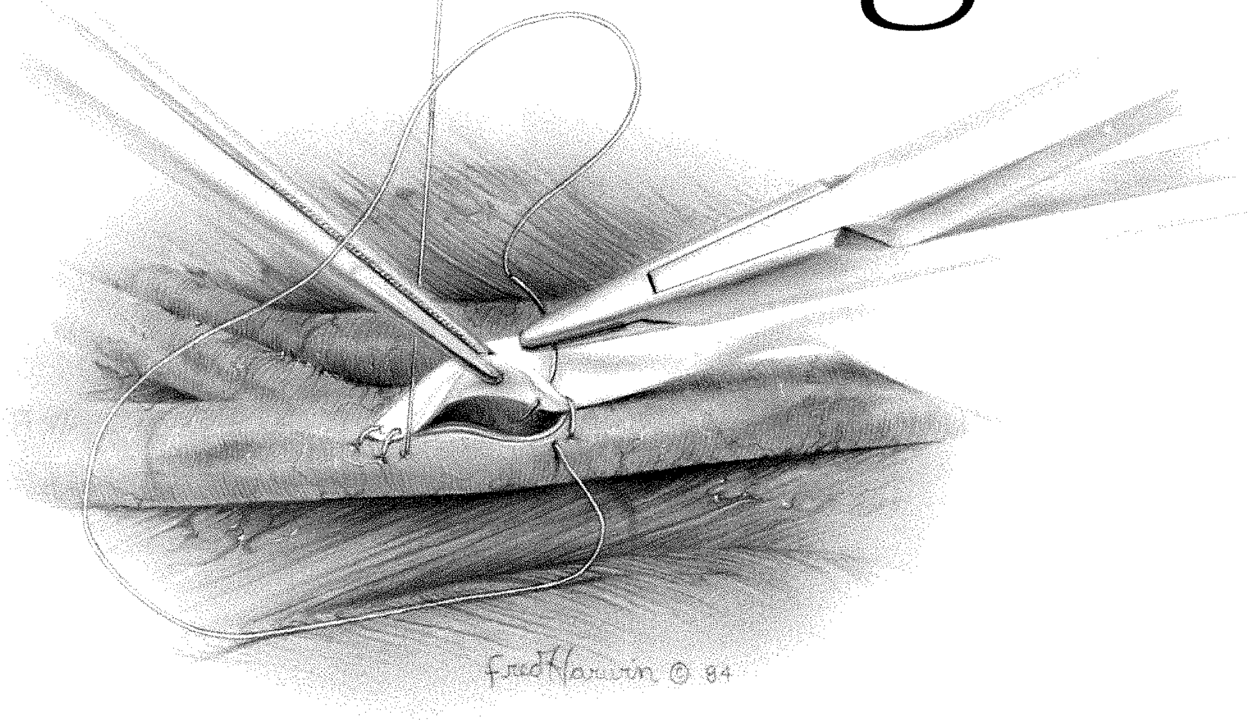

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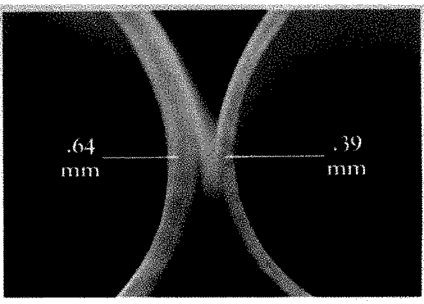

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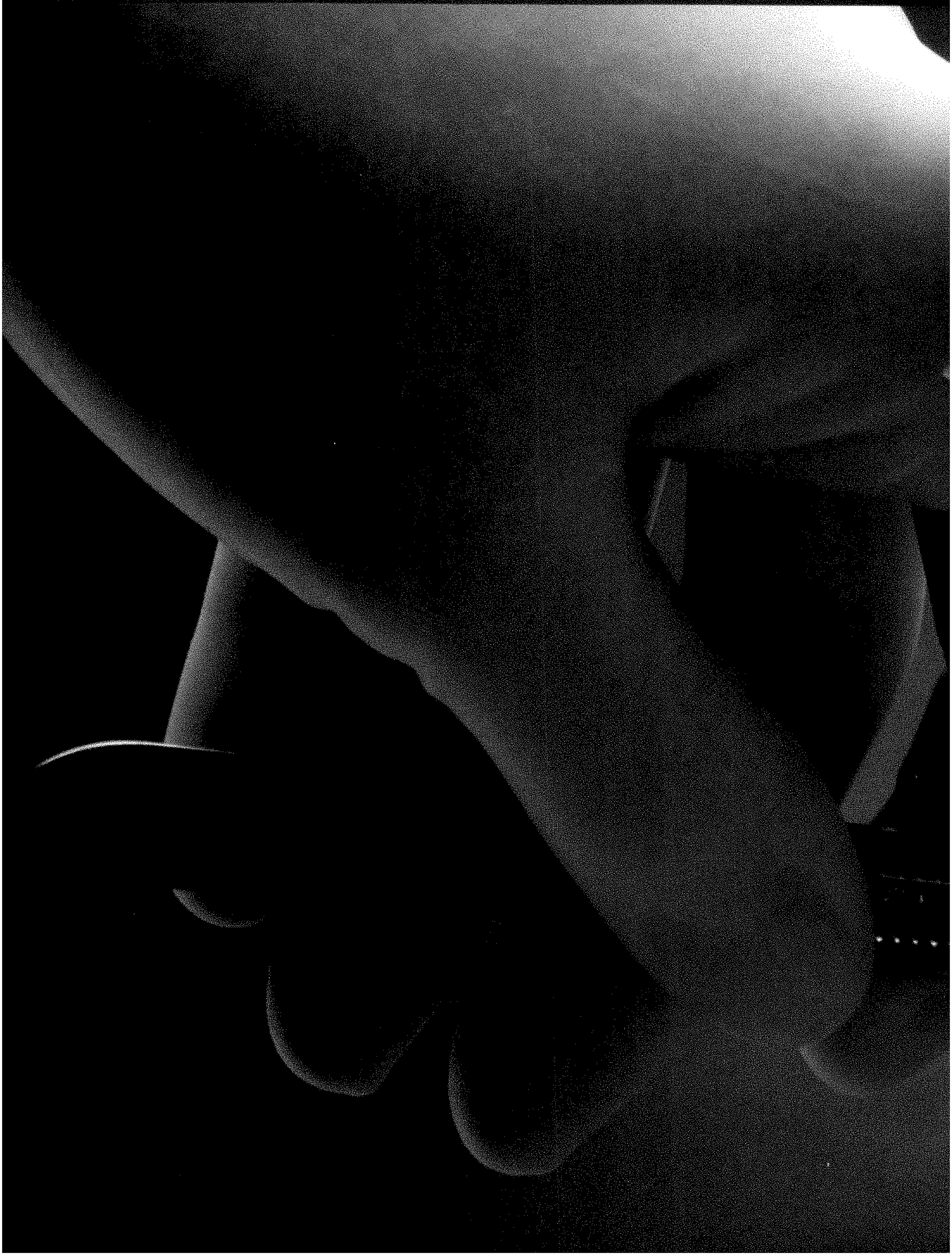

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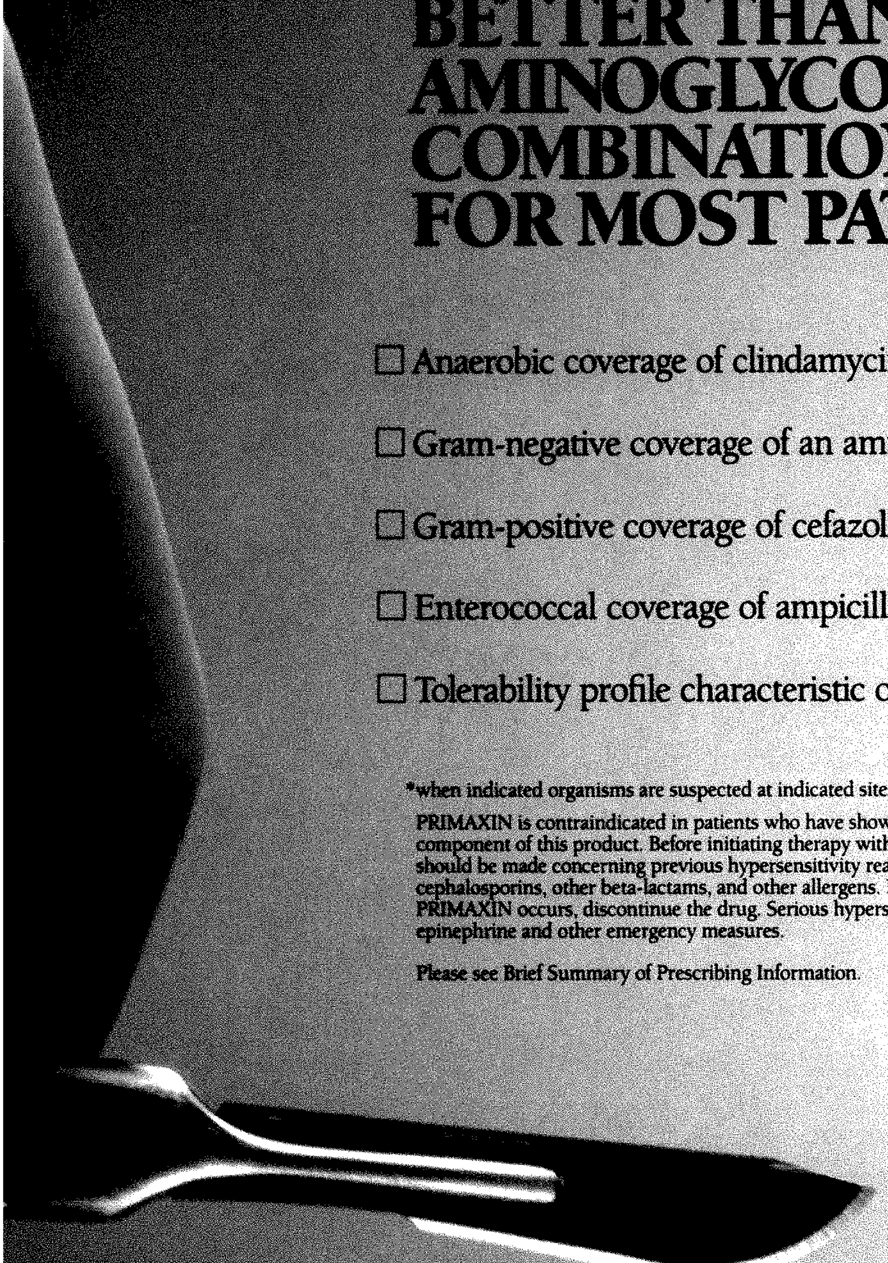

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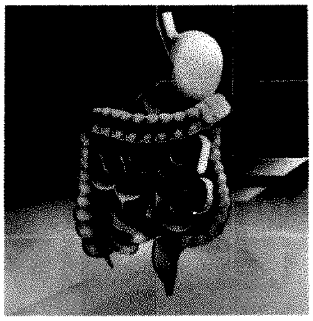

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Warnings: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH BETA LACTAMS. THESE REACTIONS ARE MORE APT TO OCCUR IN PERSONS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER BETA LACTAM. BEFORE INITIATING THERAPY WITH 'PRIMAXIN,' CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA LACTAMS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION TO 'PRIMAXIN' OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with virtually all antibiotics, including PRIMAXIN; therefore it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. This colitis may range in severity from mild to life threatening.

Mild cases of pseudomembranous colitis may respond to drug discontinuance alone. In more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte, and protein supplementation, and the use of a drug such as oral vancomycin, as indicated. Isolation of the patient may be advisable. Other causes of colitis should also be considered.

Precautions: *General*—CNS adverse experiences such as confusional states, myoclonic activity, and seizures have been reported during treatment with PRIMAXIN, especially when recommended dosages were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. However, there have been reports of CNS adverse experiences in patients who had no recognized or documented underlying CNS disorder or compromised renal function.

Patients with severe or marked impairment of renal function, whether or not undergoing hemodialysis, had a higher risk of seizure activity when receiving maximum recommended doses than those with no impairment of renal function; therefore, maximum recommended doses should be used only where clearly indicated (see DOSAGE AND ADMINISTRATION).

Patients with creatinine clearances of ≤ 5 mL/min/1.73 m^2 should not receive PRIMAXIN unless hemodialysis is instituted within 48 hours.

For patients on hemodialysis, PRIMAXIN is recommended only when the benefit outweighs the potential risk of seizures.

Close adherence to the recommended dosage and dosage schedules is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of PRIMAXIN re-examined to determine whether it should be decreased or the antibiotic discontinued.

As with other antibiotics, prolonged use of PRIMAXIN may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken. While PRIMAXIN possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system function during prolonged therapy is advisable.

Drug Interactions—Since concomitant administration of PRIMAXIN and probenecid results in only minimal increases in plasma levels of imipenem and plasma half-life, it is not recommended that probenecid be given with PRIMAXIN.

PRIMAXIN should not be mixed with or physically added to other antibiotics. However, PRIMAXIN may be administered concomitantly with other antibiotics, such as aminoglycosides.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Gene toxicity studies were performed in a variety of bacterial and mammalian tests *in vivo* and *in vitro*. The tests were: V79 mammalian cell mutation assay (PRIMAXIN alone and imipenem alone), Ames test (cilastatin sodium alone), unscheduled DNA synthesis assay (PRIMAXIN), and *in vivo* mouse cytogenicity test (PRIMAXIN). None of these tests showed any evidence of genetic damage.

Reproduction tests in male and female rats were performed with PRIMAXIN at dosage levels up to 8 times the usual human dose. Slight decreases in live fetal body weight were restricted to the highest dosage level. No other adverse effects were observed on fertility, reproductive performance, fetal viability, growth, or postnatal development of pups. Similarly, no adverse effects on the fetus or on lactation were observed when PRIMAXIN was administered to rats late in gestation.

Pregnancy—Pregnancy Category C: Teratogenicity studies with cilastatin sodium in rabbits and rats at 10 and 33 times the usual human dose, respectively, showed no evidence of adverse effect on the fetus. No evidence of teratogenicity or adverse effect on postnatal growth or behavior was observed in rats given imipenem at dosage levels up to 30 times the usual human dose. Similarly, no evidence of adverse effect on the fetus was observed in teratology studies in rabbits with imipenem at dosage levels at the usual human dose.

Teratology studies with PRIMAXIN at doses up to 11 times the usual human dose in pregnant mice and rats during the period of major organogenesis revealed no evidence of teratogenicity.

Data from preliminary studies suggest an apparent intolerance to PRIMAXIN (including emesis, inappetence, body weight loss, diarrhea, and death) at doses equivalent to the average human dose in pregnant rabbits and cynomolgus monkeys that is not seen in non-pregnant animals in these or other species. In other studies, PRIMAXIN was well tolerated in equivalent or higher doses (up to 11 times the average human dose) in pregnant rats and mice. Further studies are under way to evaluate these findings.

There are, however, no adequate and well-controlled studies in pregnant women. PRIMAXIN should be used only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRIMAXIN is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in infants and children below 12 years of age have not yet been established.

Adverse Reactions: PRIMAXIN is generally well tolerated. Many of the 1,723 patients treated in clinical trials were severely ill and had multiple background diseases and physiological impairments, making it difficult to determine causal relationship of adverse experiences to therapy with PRIMAXIN.

Local Adverse Reactions—Local adverse clinical reactions that were reported as possibly, probably, or definitely related to therapy with PRIMAXIN were: phlebitis/thrombophlebitis (3.1%), pain at the injection site (0.7%), erythema at the injection site (0.4%), vein induration (0.2%), infused vein infection (0.1%).

Systemic Adverse Reactions—The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to PRIMAXIN were: nausea (2.0%), diarrhea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%) (see PRECAUTIONS), dizziness (0.3%), pruritus (0.3%), urticaria (0.2%), somnolence (0.2%).

Additional adverse systemic clinical reactions reported as possibly, probably, or definitely drug related occurring in less than 0.2% of the patients or reported since the drug was marketed are listed within each body system in order of decreasing severity: *Gastrointestinal*—pseudomembranous colitis (see WARNINGS), hemorrhagic colitis, gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, heartburn, pharyngeal pain, increased salivation; *CNS*—encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, psychic disturbances; *Special Senses*—transient hearing loss in patients with impaired hearing, tinnitus; *Respiratory*—chest discomfort, dyspnea, hyperventilation, thoracic spine pain; *Cardiovascular*—palpitations, tachycardia; *Renal*—oliguria/anuria, polyuria; *Skin*—erythema multiforme, facial edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae; *Body as a Whole*—polyarthralgia, asthenia/weakness.

Adverse Laboratory Changes—Adverse laboratory changes without regard to drug relationship that were reported during clinical trials or reported since the drug was marketed were: *Hepatic*—increased SGPT, SGOT, alkaline phosphatase, bilirubin, and LDH; *Hemic*—increased eosinophils, positive Coombs test, decreased WBC and neutrophils, including agranulocytosis, increased WBC, increased platelets, decreased platelets, decreased hemoglobin and hematocrit, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils; *Electrolytes*—decreased serum sodium, increased potassium, increased chloride; *Renal*—increased BUN, creatinine; *Urinalysis*—presence of urine protein, urine red blood cells, urine white blood cells, urine casts, urine bilirubin, and urine urobilinogen.

NOTE: Due to the high antimicrobial activity of PRIMAXIN, it is recommended that the maximum total daily dosage not exceed 50 mg/kg/day or 4.0 g/day, whichever is lower.

How Supplied: PRIMAXIN is supplied as a sterile powder mixture in vials, infusion bottles, and single-dose ADD-Vantage®† vials containing imipenem anhydrous and cilastatin sodium as follows: 250 mg imipenem equivalent and 250 mg cilastatin equivalent; 500 mg imipenem equivalent and 500 mg cilastatin equivalent.

Caution: The suspension from vials is not for direct infusion.

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Publication of the Proceedings of the Southern Surgical Association

DAVID C. SABISTON, JR., M.D.

From the Department of Surgery, Duke University Medical Center, Durham, North Carolina

THE FIRST VOLUME of the *Transactions of the Southern Surgical Association* records the session held in Birmingham, Alabama, December 4–6, 1888 (Fig. 1). Attention is called to the fact that the Association was organized in 1887 and was first named the Southern Surgical and Gynecological Association. A review of this volume, with its 318 pages, is a fascinating experience because it is rich in the surgical thought and practices held in the United States a century ago. It was published by the Caldwell Printing Company in Birmingham, Alabama in 1889, the year after the first session, and the title page of the first issue of the *Transactions* is shown in Figure 2. Features that appear in Volume I include the Minutes of the first annual session which was held on Tuesday, December 4, 1888. The meeting was called to order at 10:00 A.M. by the President, Dr. W. D. Haggard of Nashville, with 41 members and more than 50 visitors in attendance (Fig. 3).

The Mayor of Birmingham, the Honorable A. O. Lane, delivered the Welcoming Address and he said: "Gentlemen of the Southern Surgical and Gynecological Association:—Perhaps there is no duty to which the chief magistrate of a city turns with more genuine pleasure from the cares and burdens of official life than that of extending greetings to the city's guests; and, on this occasion, that pleasure is greatly heightened by the presence of a body of men whose lives are devoted to mitigating human suffering and preserving human life. A profession glowing with such benignant aims and illustrated by the heroic self-sacrifice of the great body of its members finds a warm place in the hearts of a generous and appreciative public. Therefore, as the organ of open-handed, warm-hearted Birmingham, I bid you doubly welcome and extend to you the cordial hospitalities of the people."

After the Business Meeting that morning, Dr. J. D. S. Davis, Chairman of the Committee on Arrangements, described the Scientific Program which had been prepared by the Committee. It is interesting that local hosts and officials of Birmingham apparently had planned a number of special events in addition to the scientific sessions, since Dr. Davis reported: "The Association, however, had to decline a number of excursions which had been arranged by the local committee, as time would not permit their acceptance." At the Business Meeting, Dr. Bedford Brown moved that the membership of the Association be limited to 100 and this was referred to the Judicial Council. The Scientific Session then proceeded with the annual address of President Haggard.

It is interesting that the first page contains a notice stating, "The Committee of Publication, after due consideration, decided that it would not be wise to attempt to include the discussions of papers in the volume of Transactions, since it was impossible to get a satisfactory report of the discussions from the members after they had returned to their homes. Hereafter the Association will have a stenographer, and a full report of all discussions will be preserved." This is a very significant comment, since those who have attended the annual meetings of the Southern Surgical Association clearly recognize that the discussions form an extraordinarily important part of the scientific program. The following year, the prediction that a stenographer would be present was fulfilled, and since then the printed discussion has always been recorded in detail. In fact, the discussions are at times longer than the original paper. The

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Presented at the 100th Anniversary Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 6–9, 1987.

Reprint requests: David C. Sabiston, Jr., M.D., Department of Surgery, Duke University Medical Center, Durham, NC 27710.

Submitted for publication: December 10, 1987.

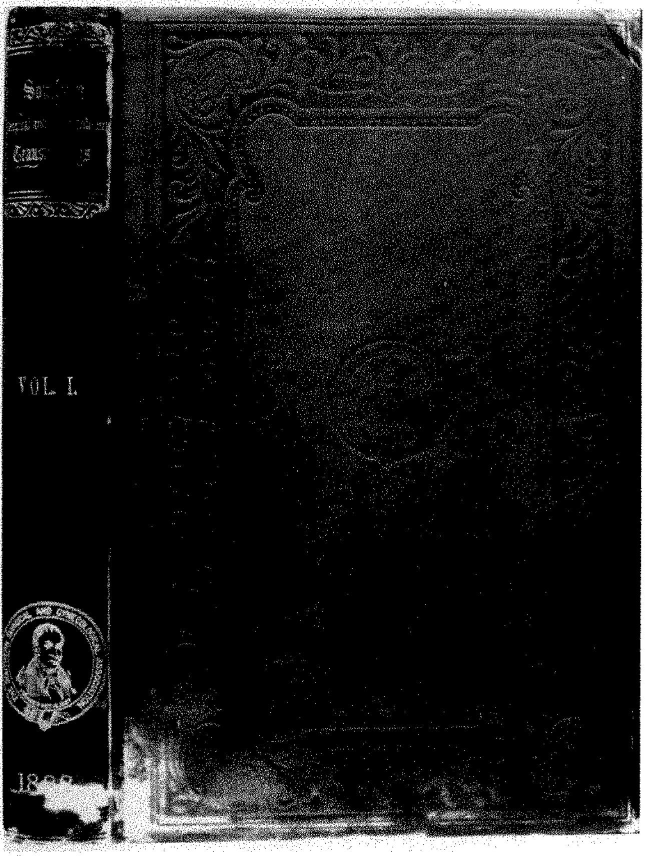


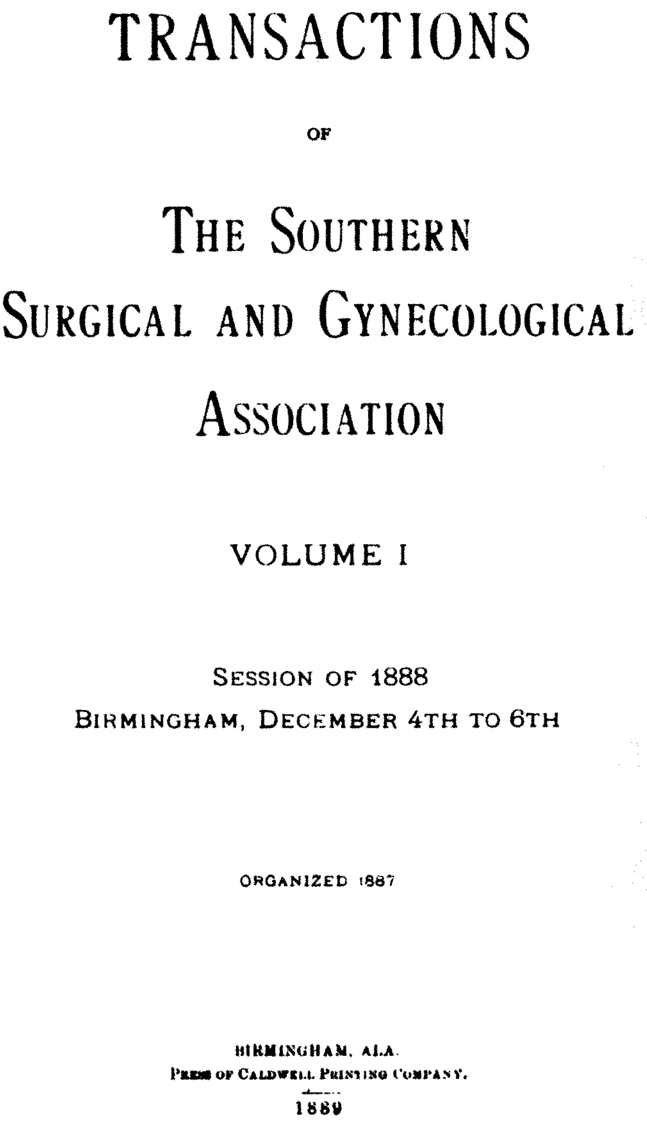
FIG. 1. Volume I of *Transactions* (from *Transactions of the Southern Surgical and Gynecological Association,* Volume I, 1888).

content of the discussions of that day was outstanding, and this feature has continued as a characteristic hallmark of the Association to the present.

The second page of Volume I of the *Transactions* lists the officers for the year 1888–1889 with Hunter McGuire as President (Fig. 4). It will be recalled that he was at the time generally regarded as the most outstanding surgeon in the South, having been a medical officer in the Confederate Army during the War between the States and the surgeon to General T. J. "Stonewall" Jackson. As has continued to the present day, in the original choice of officers, considerable attention was given both to the professional stature of those selected and recognition of geographic location. In the list of officers shown in Figure 4, the states of Tennessee, Virginia, Georgia, Alabama, Mississippi, and Kentucky are each represented.

The second annual meeting of the Association was held in Nashville on Tuesday, Wednesday, and Thursday, November 12, 13, and 14, 1889 (Fig. 5). Dr. Hunter McGuire delivered the Presidential Address at the *evening session* following the annual dinner, and it was described as being "heartily applauded" (Fig. 6). It is to be assumed that it was a delightful occasion, and perhaps a lengthy one, and most likely filled with a great deal of camaraderie since the Morning Session on the next day did not begin until 10:00 A.M.

In this Address Hunter McGuire referred to some of his experiences in the War between the States saying: "Many of the medical officers of this Corps were wounded or killed on the field. One, I saw fall at Strasburg, amid the cheers of soldiers at the evidence he gave of devotion to duty; another at Sharpsburg, facing an assault before which even veterans quailed and fled; and a third I found upon the bloody field of Cold Harbor, dying with a shell-wound through his side. As I knelt down beside him and told him his wound was mortal, he answered, 'I am no more afraid to die than I was afraid to do my duty'." One can easily understand why a reader of this Address many years ago was moved to pencil the word "Great" in the margin.



TRANSACTIONS

OF

THE SOUTHERN

SURGICAL AND GYNECOLOGICAL

ASSOCIATION

VOLUME I

SESSION OF 1888

BIRMINGHAM, DECEMBER 4TH TO 6TH

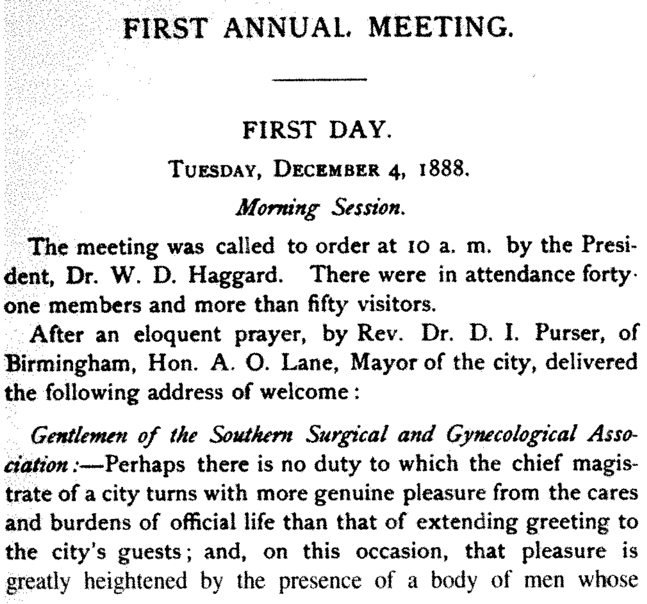
ORGANIZED 1887

BIRMINGHAM, ALA.

PRESS OF CALDWELL PRINTING COMPANY.

1889

FIG. 2. Title page, Volume I (from *Transactions of the Southern Surgical and Gynecological Association,* Volume I, 1888).



FIRST ANNUAL MEETING.

FIRST DAY.

TUESDAY, DECEMBER 4, 1888.

Morning Session.

The meeting was called to order at 10 a. m. by the President, Dr. W. D. Haggard. There were in attendance forty-one members and more than fifty visitors.

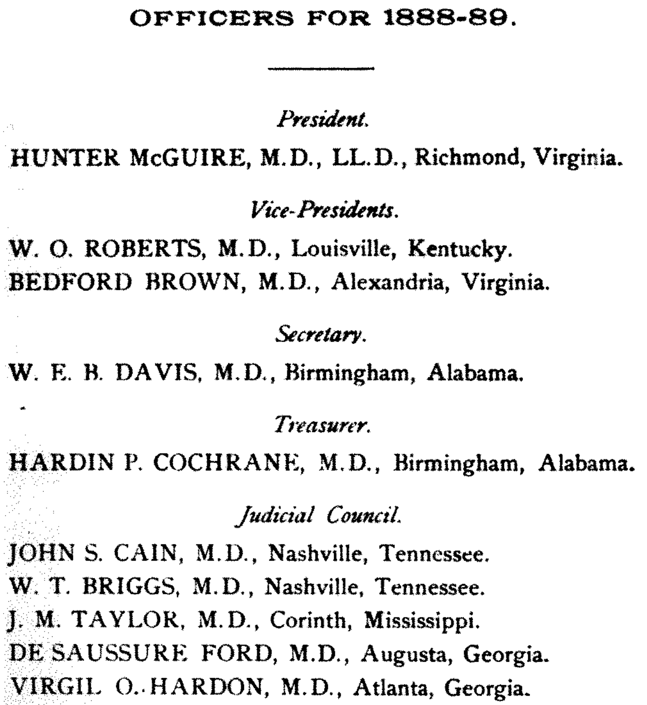
After an eloquent prayer, by Rev. Dr. D. I. Purser, of Birmingham, Hon. A. O. Lane, Mayor of the city, delivered the following address of welcome:

Gentlemen of the Southern Surgical and Gynecological Association:—Perhaps there is no duty to which the chief magistrate of a city turns with more genuine pleasure from the cares and burdens of official life than that of extending greeting to the city's guests; and, on this occasion, that pleasure is greatly heightened by the presence of a body of men whose

FIG. 3. First Annual Meeting, First Day (from *Transactions of the Southern Surgical and Gynecological Association,* Volume I, 1888).

Although the first volume of the *Transactions* was published in Birmingham, all subsequent issues of the *Transactions* through the year 1931 were published by the Dornan Printers in Philadelphia. This company used the same binding and format throughout the entire period. In retrospect, it is fascinating that this annual volume of the *Transactions* was the *only* recording of the scientific proceedings of the Southern Surgical Association to be published. In addition to the Presidential Addresses and the Minutes of the Business Meetings, all scientific papers with the discussions were recorded in them for each session. Copies of the *Transactions* were sent to the membership, as well as to medical libraries in this country and in Europe, but the annual distribution never exceeded 300 copies. It is apparent that much important surgical data were made available only to a relatively small readership.

At the 41st annual meeting of the Association in 1928, the significance of the limited coverage given the annual scientific program was discussed by the Council.



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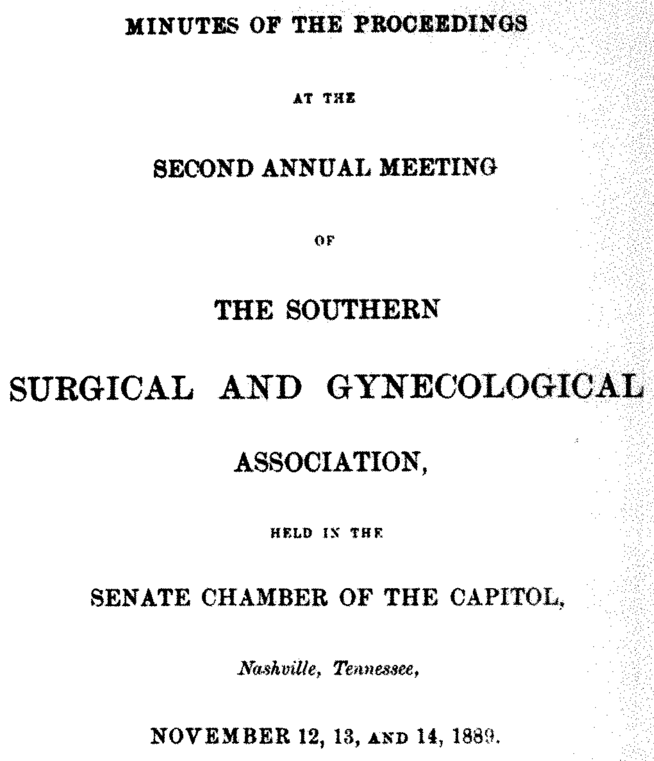
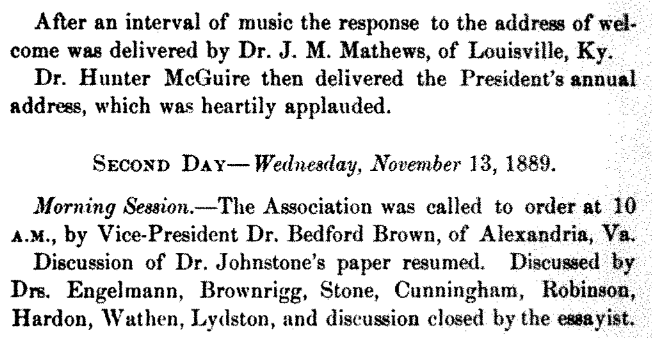
VIRGIL O. HARDON, M.D., Atlanta, Georgia.

FIG. 4. Officers for 1888–89 (from *Transactions of the Southern Surgical and Gynecological Association,* Volume I, 1888).



MINUTES OF THE PROCEEDINGS
AT THE
SECOND ANNUAL MEETING
OF
THE SOUTHERN
SURGICAL AND GYNECOLOGICAL
ASSOCIATION,
HELD IN THE
SENATE CHAMBER OF THE CAPITOL,
Nashville, Tennessee,
NOVEMBER 12, 13, AND 14, 1889.

FIG. 5. Second Annual Meeting (from *Transactions of the Southern Surgical and Gynecological Association,* Volume II, 1889).



After an interval of music the response to the address of welcome was delivered by Dr. J. M. Mathews, of Louisville, Ky.

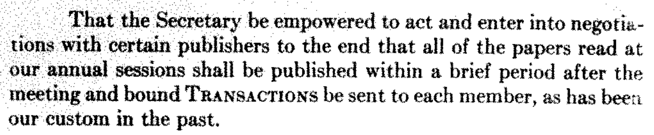
Dr. Hunter McGuire then delivered the President's annual address, which was heartily applauded.

SECOND DAY—*Wednesday, November* 13, 1889.

Morning Session.—The Association was called to order at 10 A.M., by Vice-President Dr. Bedford Brown, of Alexandria, Va.

Discussion of Dr. Johnstone's paper resumed. Discussed by Drs. Engelmann, Brownrigg, Stone, Cunningham, Robinson, Hardon, Wathen, Lydston, and discussion closed by the essayist.

FIG. 6. Minutes, Second Annual Meeting (from *Transactions of the Southern Surgical and Gynecological Association,* Volume II, 1889).



That the Secretary be empowered to act and enter into negotiations with certain publishers to the end that all of the papers read at our annual sessions shall be published within a brief period after the meeting and bound TRANSACTIONS be sent to each member, as has been our custom in the past.

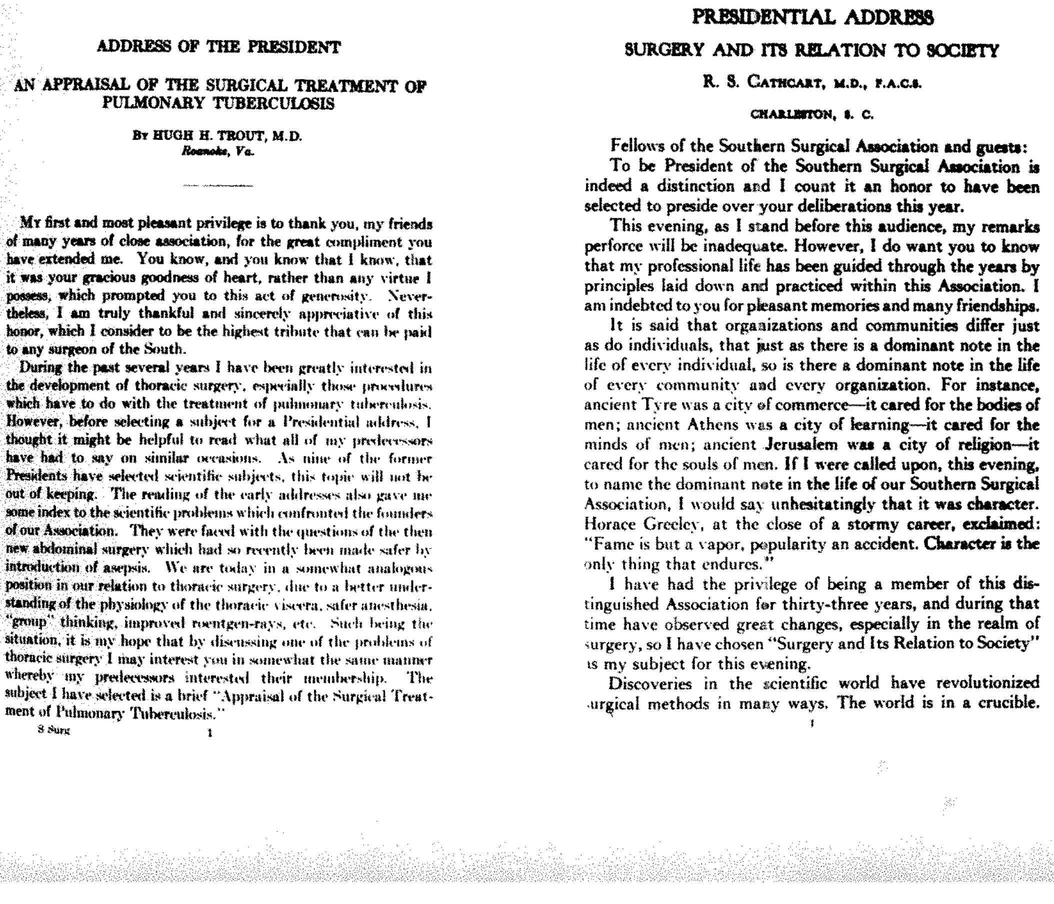
FIG. 7. 41st Annual Meeting resolution (from *Transactions of the Southern Surgical Association,* Volume 41, 1928).

In the Minutes of this meeting, one finds the following resolution: "That the Secretary be empowered to act and enter into negotiations with certain publishers to the end that all of the papers read at our annual scientific sessions shall be published within a brief period after the meeting and bound *Transactions* be sent to each member, as has been our custom in the past" (Fig. 7). Apparently little transpired during that year because the Minutes of the following annual session contained the statement: "That your Secretary continue to negotiate with certain publishers, etc." Progress was slow in making these arrangements originally recommended by the Council, and 3 years later, in 1932, it was recorded in the Minutes: "That the proposition made to the Southern Surgical Association by the *American Journal of Surgery* be accepted, and that the *American Journal of Surgery* be adopted as the official organ of the Southern Surgical Association for the publication of all papers read, together with the issuance of the *Transactions.*" This recommendation was adopted by the Association, and for the next 3 years the *Transactions* were printed by Paul B. Hoeber, Inc. of New York, the publishers of the *American Journal of Surgery.*

Although the size of the volumes was approximately the same as those previously prepared by the Dornan Company, the print was different (Fig. 8) than the type used in the last issue published by the Dornan Company shown on the left and that by Paul B. Hoeber, Inc. in 1932 on the right. During these years, most of the papers presented at the annual meeting were published in the *American Journal of Surgery* in its May and June issues.

In 1934, a youthful and dynamic figure who was subsequently to achieve worldwide acclaim, Alton Ochsner of New Orleans, was elected as Secretary of the Southern Surgical Association, being only the fifth elected to this office in the 48 years since the founding of the Association (Fig. 9). In 1935, the *Transactions* was published by the J. B. Lippincott Company of Philadelphia, and since then this relationship has been maintained for over half a century.

As had occurred previously, there was a slight change in format between the last issue of the *Transactions* by Hoeber and the first by Lippincott (Fig. 10). Since then, papers presented at the Southern Surgical Association have appeared in *Annals of Surgery* in the May and June issues. In Volume 103, January–June, 1936, the masthead read: "Annals of Surgery—Also the Official Publication of the American Surgical Association and of the Southern Surgical Association." One of the greatest secretaries of the Southern Surgical Association, Alton Ochsner, arranged for publication of a separate index



ADDRESS OF THE PRESIDENT

AN APPRAISAL OF THE SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS

BY HUGH H. TROUT, M.D.
Roanoke, Va.

MY first and most pleasant privilege is to thank you, my friends of many years of close association, for the great compliment you have extended me. You know, and you know that I know, that it was your gracious goodness of heart, rather than any virtue I possess, which prompted you to this act of generosity. Nevertheless, I am truly thankful and sincerely appreciative of this honor, which I consider to be the highest tribute that can be paid to any surgeon of the South.

During the past several years I have been greatly interested in the development of thoracic surgery, especially those procedures which have to do with the treatment of pulmonary tuberculosis. However, before selecting a subject for a Presidential address, I thought it might be helpful to read what all of my predecessors have had to say on similar occasions. As nine of the former Presidents have selected scientific subjects, this topic will not be out of keeping. The reading of the early addresses also gave me some index to the scientific problems which confronted the founders of our Association. They were faced with the questions of the then new abdominal surgery which had so recently been made safer by introduction of asepsis. We are today in a somewhat analogous position in our relation to thoracic surgery, due to a better understanding of the physiology of the thoracic viscera, safer anesthesia, "group" thinking, improved roentgen-rays, etc. Such being the situation, it is my hope that by discussing one of the problems of thoracic surgery I may interest you in somewhat the same manner whereby my predecessors interested their membership. The subject I have selected is a brief "Appraisal of the Surgical Treatment of Pulmonary Tuberculosis."

8 Surg 1

PRESIDENTIAL ADDRESS

SURGERY AND ITS RELATION TO SOCIETY

R. S. CATHCART, M.D., F.A.C.S.

CHARLESTON, S. C.

Fellows of the Southern Surgical Association and guests:

To be President of the Southern Surgical Association is indeed a distinction and I count it an honor to have been selected to preside over your deliberations this year.

This evening, as I stand before this audience, my remarks perforce will be inadequate. However, I do want you to know that my professional life has been guided through the years by principles laid down and practiced within this Association. I am indebted to you for pleasant memories and many friendships.

It is said that organizations and communities differ just as do individuals, that just as there is a dominant note in the life of every individual, so is there a dominant note in the life of every community and every organization. For instance, ancient Tyre was a city of commerce—it cared for the bodies of men; ancient Athens was a city of learning—it cared for the minds of men; ancient Jerusalem was a city of religion—it cared for the souls of men. If I were called upon, this evening, to name the dominant note in the life of our Southern Surgical Association, I would say unhesitatingly that it was character. Horace Greeley, at the close of a stormy career, exclaimed: "Fame is but a vapor, popularity an accident. Character is the only thing that endures."

I have had the privilege of being a member of this distinguished Association for thirty-three years, and during that time have observed great changes, especially in the realm of surgery, so I have chosen "Surgery and Its Relation to Society" as my subject for this evening.

Discoveries in the scientific world have revolutionized surgical methods in many ways. The world is in a crucible.

1

FIG. 8. Dornan Company (on left) vs. Hoeber, Inc. (on right) (from *Transactions of the Southern Surgical Association,* Volume 44, 1931 and *Transactions of the Southern Surgical Association,* Volume 45, 1932).

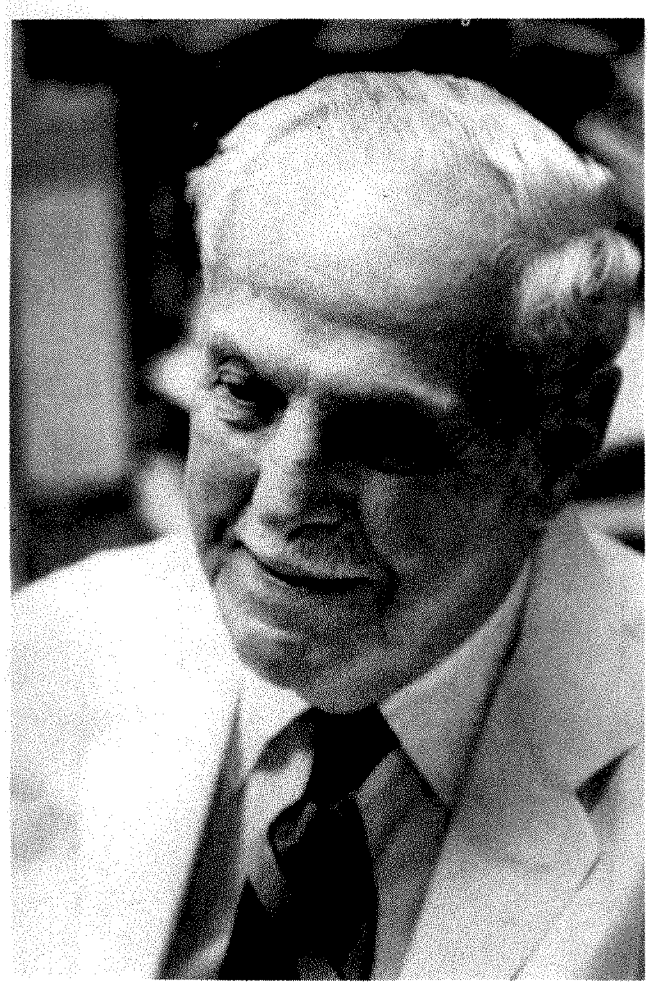
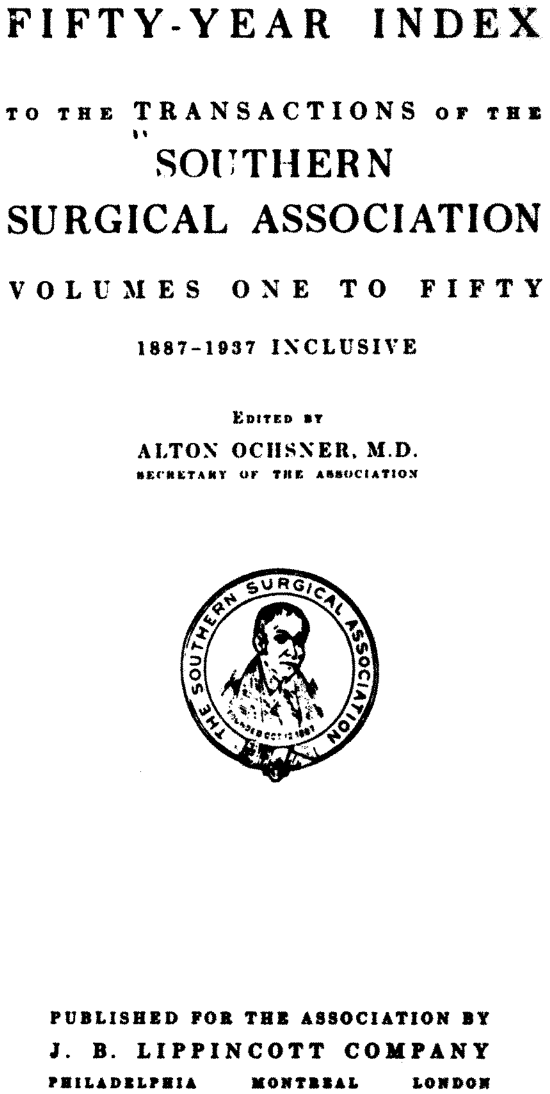


FIG. 9. Alton Ochsner.



FIFTY-YEAR INDEX

TO THE TRANSACTIONS OF THE

SOUTHERN

SURGICAL ASSOCIATION

VOLUMES ONE TO FIFTY

1887-1937 INCLUSIVE

EDITED BY

ALTON OCHSNER, M.D.

SECRETARY OF THE ASSOCIATION

PUBLISHED FOR THE ASSOCIATION BY

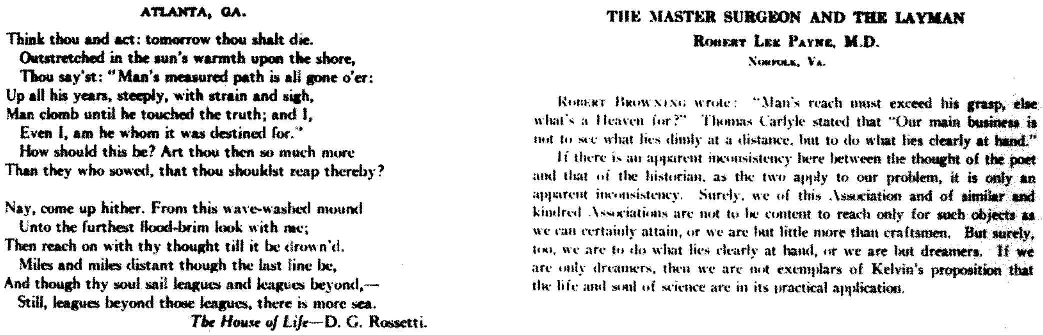
J. B. LIPPINCOTT COMPANY

PHILADELPHIA MONTREAL LONDON

FIG. 11. Index of 1st 50 years of *Transactions* (from *Fifty-Year Index to the Transactions of the Southern Surgical Association*, 1940).

summarizing the recordings of the *Transactions* for the first 50 years. This volume was published in 1940 with 133 pages and the subject and author headings were combined into an index and published by the J. B. Lippincott Company (Fig. 11).

The meeting of 1942 was cancelled because of World War II when professional meetings were withheld at the request of the Federal Government. In 1943, the Southern Surgical Association resumed its annual meeting, and the 55th session was held at the Roosevelt Hotel in



PRESIDENTIAL ADDRESS
PROGRESS IN SURGERY

FRANK K. BOLAND, M.D.

ATLANTA, GA.

Think thou and act: tomorrow thou shalt die.
  Outstretched in the sun's warmth upon the shore,
  Thou say'st: "Man's measured path is all gone o'er:
Up all his years, steeply, with strain and sigh,
Man clomb until he touched the truth; and I,
  Even I, am he whom it was destined for."
  How should this be? Art thou then so much more
Than they who sowed, that thou shouldst reap thereby?

Nay, come up hither. From this wave-washed mound
  Unto the furthest flood-brim look with me;
Then reach on with thy thought till it be drown'd.
  Miles and miles distant though the last line be,
And though thy soul sail leagues and leagues beyond,—
  Still, leagues beyond those leagues, there is more sea.

The House of Life—D. G. Rossetti.

PRESIDENTIAL ADDRESS

THE MASTER SURGEON AND THE LAYMAN

ROBERT LEE PAYNE, M.D.

NORFOLK, VA.

ROBERT BROWNING wrote: "Man's reach must exceed his grasp, else what's a Heaven for?" Thomas Carlyle stated that "Our main business is not to see what lies dimly at a distance, but to do what lies clearly at hand."

If there is an apparent inconsistency here between the thought of the poet and that of the historian, as the two apply to our problem, it is only an apparent inconsistency. Surely, we of this Association and of similar and kindred Associations are not to be content to reach only for such objects as we can certainly attain, or we are but little more than craftsmen. But surely, too, we are to do what lies clearly at hand, or we are but dreamers. If we are only dreamers, then we are not exemplars of Kelvin's proposition that the life and soul of science are in its practical application.

FIG. 10. Hoeber, Inc. (on left) vs. Lippincott (on right) (from *Transactions of the Southern Surgical Association*, Volume 47, 1934 and *Transactions of the Southern Surgical Association*, Volume 48, 1935).

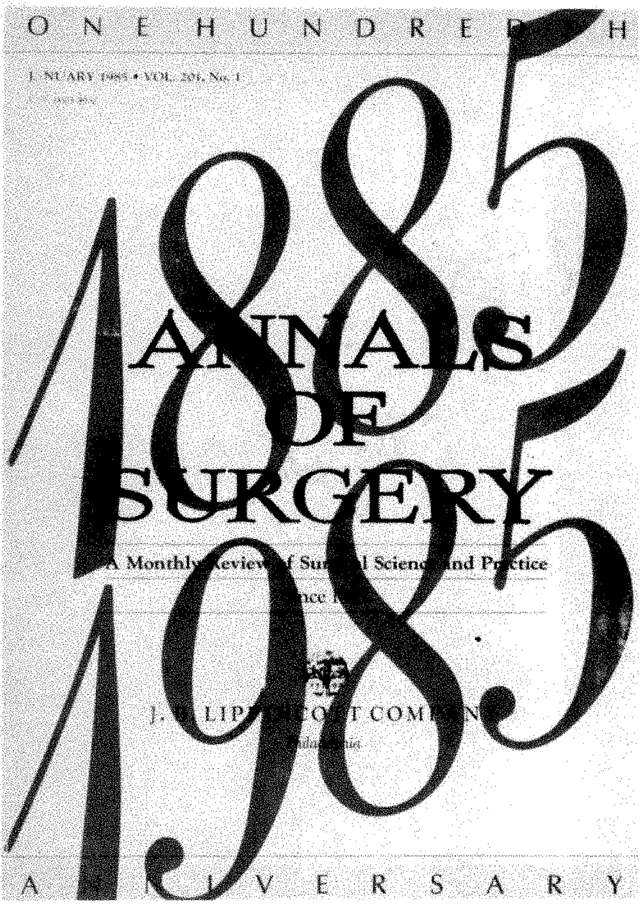
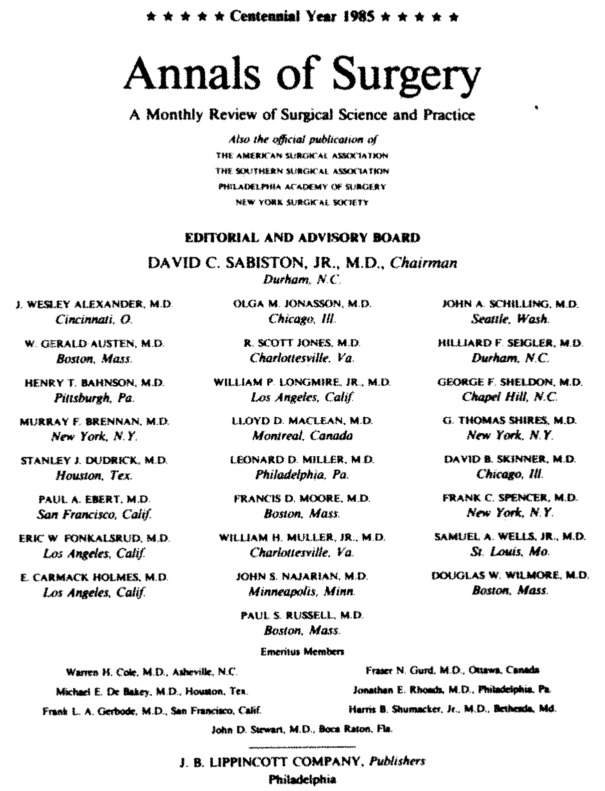


FIG. 12. Cover page of *Annals of Surgery* Centennial Year (from *Annals of Surgery*, Volume 201:1, 1985).

New Orleans with 125 members present. Alton Ochsner was elected President that year and Alfred Blalock became the new Secretary.

In 1985, *Annals of Surgery* celebrated its Centennial and used a somewhat different format for the cover page for the 12 months in that year (Fig. 12). *Annals of Surgery* first appeared in January 1885, and today it is recognized as the oldest journal published in English devoted exclusively to surgery. On the first page of the Centennial issue, one finds the Statement of the Publisher, Mr. John Wehner, who said: "This year, 1985, is *Annals of Surgery*'s 100th birthday. It is a remarkable achievement for a medical journal to have bridged a span of 100 years of change and to have maintained a position of eminence and leadership over the past century of surgical progress." Further in this commentary, he paid great tribute to the members of the Editorial Board who, as he said, "review every manuscript" as well as those who form the editorial process.

The Editorial Board of *Annals of Surgery* has been fortunate to have among its members through the past century a number of outstanding master surgeons and unquestioned leaders in the field. Of interest to members of the Southern Surgical Association is the fact that currently 17 of the members of the Editorial Board are also members of the Southern Surgical Association (Fig. 13). This emphasizes both the significance of the Southern Surgical Association and the recognition it receives by *Annals of Surgery*, as well as the fact that this Association has from its outset maintained a policy of selection of members from outstanding figures in surgery *throughout the nation* and not solely those from the Southern States. In this connection, it is interesting to review the issue of *Transactions* that recorded the 1890 meeting in Atlanta in which one finds the following statement by R. B. Maury of Memphis: ". . . This society, as its name implies, is distinctively Southern, but it is not exclusively so, for it has opened wide its doors with a hearty welcome to distinguished men of ability from all sections of our common country. Its membership, although it is now only in the third year of its existence, has reached the phenomenal growth of 100 members, and among those members I may say that we are proud to claim some of the most distinguished men to be found in the ranks of surgery and gynecology." Through the years, the entire membership has recognized the significance of this point of view in providing



★ ★ ★ ★ ★ **Centennial Year 1985** ★ ★ ★ ★ ★

Annals of Surgery

A Monthly Review of Surgical Science and Practice

Also the official publication of
THE AMERICAN SURGICAL ASSOCIATION
THE SOUTHERN SURGICAL ASSOCIATION
PHILADELPHIA ACADEMY OF SURGERY
NEW YORK SURGICAL SOCIETY

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Philadelphia

FIG. 13. Editorial Board, *Annals of Surgery* (from *Annals of Surgery*, Volume 201:1, 1985).

great strength, depth, and breadth at the annual scienific meetings of the Southern Surgical Association.

Also in the first issue of the Centennial Year of *Annals of Surgery* is a commentary on "The First 100 Years: Annals of Surgery and a Century of Progress." The hisory of the founding of *Annals of Surgery* is noted to have begun as a concept of Lewis S. Pilcher. The title page of the first issue of *Annals of Surgery* in 1885 is shown in Figure 14. Pilcher was a remarkable individual, a tireless worker who early brought prominence to he Journal (Fig. 15).

It is interesting that early in 1885 the *Canadian Medical and Surgical Journal* stated editorially: "We have received the prospectus of a new medical monthly called he *Annals of Surgery.* It is to be devoted entirely to surgery and it is intended to be representative of the surgical thought and work of the present day. The Journal will appear on the first day of each month, simultaneous in the United States and Great Britain. This is the first attempt, as far as we know, to publish in the English language, a periodical exclusively devoted to surgery. We wish the enterprise every success and feel sure that it will be supported by both British and American surgeons."

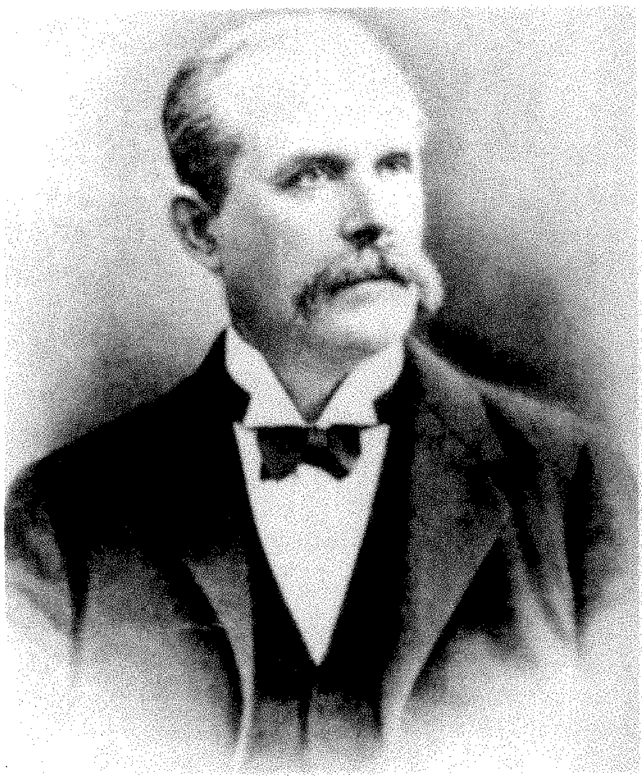
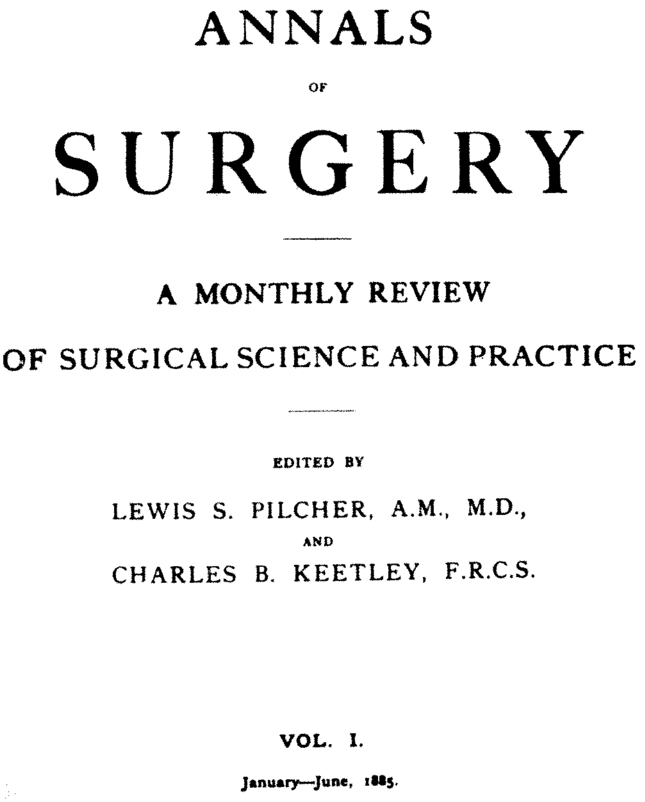


FIG. 15. Lewis S. Pilcher, 1900, age 55 (from *Annals of Surgery,* Volume 201:1, 1985).



ANNALS

OF

SURGERY

A MONTHLY REVIEW

OF SURGICAL SCIENCE AND PRACTICE

EDITED BY

LEWIS S. PILCHER, A.M., M.D.,

AND

CHARLES B. KEETLEY, F.R.C.S.

VOL. I.

January—June, 1885.

FIG. 14. Title page, 1st issue of *Annals of Surgery,* 1885 (from *Annals of Surgery,* Volume 201:1, 1985).

Since 1897, the sole publisher of *Annals of Surgery* has been the J. B. Lippincott Company, which is thoroughly committed to the highest standards of publishing with an established policy of maintaining excellence in every aspect of the field. The firm has entrusted complete responsibility for the decision-making process concerning manuscripts accepted for publication entirely to the Editorial Board. It is remarkable that in the first 6 issues of *Annals of Surgery* there were a total of 51 authors, 22 of whom were from the British Isles and Canada. Among the contributors was Lewis Atterbury Stimson, the noted Professor of Surgery at Columbia University and Presbyterian Hospital in New York, who reviewed the use of the ligature in the treatment of aneurysms. On the 20th anniversary of *Annals of Surgery,* the *Montreal Medical Journal* noted: "The December issue of the *Annals of Surgery* sustains a verdict that it achieved an undisputed place as a leading exponent of surgery in the English language. This issue signalizes the close of the first 20 years of publication of this journal, and the publishers have properly marked the event by issuing a Festschrift number, which is more than double the annual size, and is remarkable for the value of its contents, the number and quality of its contributors, and the abundance and quality of its illustrations."

It is further remarkable that Lewis Pilcher was Editor for 50 continuous years and is seen in Figure 16 in his later years (1930). Shortly after he had completed the

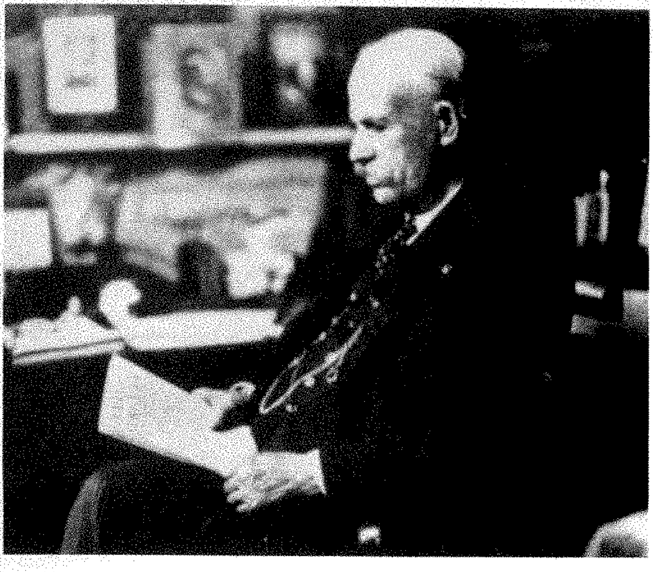


FIG. 16. Lewis S. Pilcher, 1930, age 85 (from *Annals of Surgery,* Volume 201:1, 1985).

December issue of 1934, he died quietly, having led the Journal so effectively for a remarkable period.

As *Annals of Surgery* enters its second century, and 52nd year of publishing the *Transactions of the Southern Surgical Association,* the Journal is currently being sent to subscribers in 117 nations around the world. Each year the May and June issues are exceedingly strong, recording as they do the scientific papers presented at this Annual Meeting. The same is true of the September and October issue each year as these contain the presentations made at the Annual Meeting of the American Surgical Association.

Reflecting on all issues of the *Transactions* during the past century, it is obvious that the Southern Surgical Association has been the site of extraordinary accounts of major advances in surgery as well as reviews of the state of the art at different periods. Today, it is difficult to obtain a complete series of the *Transactions,* as might well be expected, but fortunately, a number are present in libraries throughout the nation. From inception to the present, the Southern Surgical Association has been a highly revered and respected annual surgical scientific session with the highest standards of scientific excellence. *Tradition* is a very important part of this very special organization—but, the leadership and membership alike have always known that, as T. S. Eliot so wisely said: "Tradition cannot be inherited, and if you want it you must obtain it by *great* labor." All members can take much pride in our surgical heritage as the Southern Surgical Association approaches the second century of this *great,* and distinctively *unique,* organization and will surely continue to *work* for it and its annual scientific sessions in the future as in the past.

The Collection and Preservation of the Archives of the Southern Surgical Association

ROBERT S. SPARKMAN, M.D., LL.D.

From the Department of Surgery, Baylor University Medical Center, Dallas, Texas

THE COUNCIL OF THE SOUTHERN SURGICAL ASSOCIATION, in 1891, in anticipation of its forthcoming centenary in 1987, recommended the appointment of a committee that was given the responsibility of making plans for the celebration and commemoration of that event. The following year a committee of three was named for this purpose, consisting of Drs. David C. Sabiston of Durham, G. Rainey Williams of Oklahoma City, and Robert S. Sparkman of Dallas as chairman. Dr. J. D. Martin of Atlanta was appointed as a special consultant to the committee, and a year later Dr. Laman A. Gray, Sr. of Louisville was also added.

In 1984, the committee was given the additional responsibility of seeking and arranging for a university library to serve as the permanent repository for the archives of the Association. It was understood that an additional duty of the committee would be to search for and to assemble the items of historical interest that would comprise the organizational archive.

As is so often the case in scientific societies, there had never been any serious effort in the Southern Surgical Association to maintain a comprehensive collection of historical documents and memorabilia. From 1956 to 1965, provision had been made in the By-Laws for the office of Historian, but little if anything was accomplished and the office was soon terminated. During most of its first century, the entire scientific and historical record of the Association was contained in the programs, the attendance rosters, the secretary's newsletters, the annual volume of *Transactions,* and the manuscripts published in the *American Journal of Surgery* (1932, 1933 and 1934 meetings) or in *Annals of Surgery* (1935 meeting to the present).

Collection of the Archives

In 1984, a serious effort was begun by the committee to acquire items for an archival collection. The assistance of members of the organization and their families was sought, with gratifying results. One of the first efforts was to obtain photographs of all of the presidents, from the first, W. D. Haggard of Nashville, to the current, John L. Sawyers, also of Nashville. Eventually all of them were acquired.

A search was also begun for reprints of the presidential addresses. Except for the year 1957 (the presidential year of Floyd W. McRae of Atlanta), the collection is complete for the last 33 years. However, for the first 66 years only eight reprints of presidential addresses could be located, including the following: Hunter H. McGuire, 1889; Stuart McGuire, 1909; LeGrand Guerry, 1924; Hubert A. Royster, 1926; Albert O. Singleton, 1939; Alton Ochsner, 1944; and Daniel C. Elkin, 1946.

During the first half-century of the Association, the secretary compiled the attendance roster from memory and by recognition of those present. In time this became an impossible task, and in 1938, at the beginning of the second half-century, Secretary Alton Ochsner of New Orleans instituted a signature roster, using loose leaf ledger pages. All of them have been preserved. Currently, similar pages are used to record the attendance of guests. There is no record to indicate when this practice was begun, and unfortunately these pages have been discarded or destroyed.

Presented at the 100th Anniversary Meeting of The Southern Surgical Association, Hot Springs, Virginia, December 6–9, 1987.

Reprint requests and correspondence: Robert S. Sparkman, M.D., 1004 No. Washington, Dallas, TX 75204.

Submitted for publication: January 14, 1988.

No one knows when the first programs of the scientific sessions were printed and distributed. The earliest in the archival collection is for 1926. The series is complete from 1947 to the present, a period of 41 years. Each year the secretary mails the programs to members in advance of the meeting, along with two other booklets. One of these, the Family Register, so indispensable and unique to this organization, was first published in 1952, during the secretarial term of John C. Burch of Nashville. The collection is complete except for 1954. The third booklet is the confidential list entitled Candidates for Fellowship, which also was first printed in 1952. This series is complete.

The Shipley Award of the Southern Surgical Association was instituted in 1956, and provided for the award annually of a medal to the new member judged to have given the best presentation. It was established in memory of Dr. Arthur M. Shipley, Professor of Surgery at the University of Maryland Medical School from 1920 to 1948, and member of the Association from 1927 until his death in 1955. The first recipient was Felda Hightower of Winston-Salem in 1958, for his 1957 presentation. During the 1987 meeting, Dr. Hightower formally presented his historically important medal to the Association for addition to the archival collection. Dr. George A. Hallenbeck, currently of California, winner for his presentation in 1973 during his tenure at the University of Alabama in Birmingham, also donated his medal for the same purpose, in absentia. Before the 100th anniversary meeting there had been 29 recipients of the Shipley Award. The archival collection contains photographs of all of them, and reprints or photocopies of their award-winning presentations, most of which have been autographed by the author.

Operations performed on United States Presidents during their terms of office always have been of immense public interest, both because of their enduring historical significance and because of their possible impact on national and international affairs. During his term of office, Dwight D. Eisenhower had a somewhat controversial operation for acute intestinal obstruction due to chronic regional enteritis. The operation was performed at Walter Reed Army Medical Center by Lt. Gen. Leonard Heaton, then Surgeon General of the Army. Dr. Isidor S. Ravdin of Philadelphia was flown from Chicago in Air Force One to participate in the preoperative study and the surgical procedure. Other team members included Brian Blades and General (then Lt. Col.) Thomas Whelan. All with the exception of Whelan were members of the Southern Surgical Association. In 1963, General Heaton presented a detailed report of the operation before the Association. A reprint of the presentation was subsequently sent to President Eisenhower, who graciously inscribed it and also provided an autographed photograph of himself.

Seven years later, in 1971, Maj. Gen. Carl Hughes, also a member, presented a follow-up report to the Association entitled "A Review of the late General Eisenhower's Operations." Mrs. Eisenhower, who had given her permission for this presentation, inscribed a reprint of the publication and provided an autographed photograph of herself.

In each instance the reprints were also autographed by the authors and co-authors. The complete collection will become a part of the organizational archive.

In 1904, the Association met in Birmingham, just 1 year after the accidental death of the Founder, W. E. B. Davis. In memory of Dr. Davis, a full-length bronze statue had been commissioned, to be executed by the distinguished sculptor, Giuseppe Moretti, who had achieved fame for his immense statue of Vulcan, which stands on a high bluff overlooking the city of Birmingham. In elaborate ceremonies open to the public and preceded by a parade, the Davis statue was unveiled before a large audience. A medal of identification was worn by members of the Association. The clasp bears the single word, "FELLOW," while the words "Birmingham, Dec. 13–15, 1904" are printed on the ribbon. The circular pendant is the seal of the Association, surrounded by an ornamental border. There is no mention of such a medal in the Minutes of the Association. The one such medal known to exist has been donated for the historical collection. As far as is known, this is the only occasion in the history of the Association when any sort of identification badge has ever been worn by the members.

There are other acquisitions of historical interest. One of these is a commemorative menu and banquet program of the fiftieth anniversary dinner of the Association, held at the Tutwiler Hotel in Birmingham on Wednesday evening, December 8, 1937. Another is a souvenir given to each member in 1931 by President Hugh H. Trout of Roanoke. This consists of a printed card in a narrow black frame that contains two small brick fragments. One of the fragments is identified as having come from the foundation of the "Great House" on Jamestown Island, Virginia, which served in 1628 as the first hospital in America. The other fragment came from the chimney of the building in Birmingham in which the Southern Surgical Association was organized in 1887. Two of these souvenirs are known to exist. The one that was the personal property of Dr. Trout has been donated to the Association.

Two excellent formal outdoor group photographs contributed by members depict the audience attending the 27th annual session at the Grove Park Inn in Asheville, North Carolina, in 1914, and those attending the 49th annual session at the Edgewater Gulf Hotel in Edgewater Park, Mississippi, in 1936. In the 1914 photograph the ladies are included. The collection also contains many informal photographs of the social events and the meeting places, taken by members and donated by them in response to requests of the Committee.

A recently acquired item of memorabilia is a block of marble presented to the Association by Arlie R. Mansberger of Augusta during his presidential year, 1986. It was recovered from the wall of an operating room in the old University of Maryland Hospital in which Dr. Arthur M. Shipley removed the first pheochromocytoma to have been diagnosed correctly before operation. The hospital has since been demolished.

For about 15 years nonprofessional audio tapes have been made of the presidential addresses and of the two business meetings that are regularly conducted by the Association. The second business meeting, which is the concluding event of the annual meeting, includes the presentation of the Shipley Medal, the election of new members and officers, and the response of the newly elected president. Informal photographs also have been made of these events. The cassette tapes and the photographs will become a part of the archival collection.

Selection and Designation of an Archival Repository

Early in 1985 the committee began a search for a university medical library willing to house and preserve the documents and memorabilia of the Association, and qualified to do so. Overtures were made to several institutions, each of which expressed interest in the project. However, the most enthusiastic responses came from the University of Alabama at Birmingham, the city in which the Association had been founded in 1887.

The Lister Hill Library of the University of Alabama was completed by the State in 1971. The name of the library commemorates the contributions of two generations of a distinguished Alabama family to medicine and surgery in the United States.

Lister Hill was the son of Luther Leonidas Hill, Jr., a native Alabama physician and surgeon. Luther Hill graduated in medicine from New York University, after which he trained under the elder Gross in Philadelphia and then under Joseph Lister at King's College in London. In his presidential address to the Southern Surgical Association in 1974, David C. Sabiston, Jr.[1] of Durham states that "many contributions to cardiac surgery have their origin in this country, and the first major achievement in this field was made in 1902 by Luther Leonidas Hill, Jr. of Alabama." Sabiston goes on to say that in 1902 Luther Hill performed the first successful closure of a heart wound in this country, and gives details of the injury and operation. He then adds the following: "One cannot mention the name of Hill in the United States without recognizing its more recent pertinence in the field of medicine. Dr. Luther L. Hill's son, Lister, named for Joseph Lister, was first sent to the United States Congress from Alabama at the young age of 28 and was later elected to the United States Senate in 1938. He was the original author of the Hill-Burton Act for the building of hospitals, which, together with his strong support of medical research through the National Institutes of Health, has brought the United States to first place among the nations of the world in medicine. Lister Hill served in Congress for 45 years and was consistently a champion of medical education, research, and patient care."

In 1985, an extensive correspondence was begun with Dr. Arnold G. Diethelm, Chairman of the Department of Surgery at UAB with Dr. Charles A. McCallum, then Senior Vice President for Health Affairs and now President of the University, and with other Birmingham members of the Southern Surgical Association. At the invitation of Drs. Diethelm and McCallum, the committee chairman visited the university and the Lister Hill Library in March 1986.

The handsome library is attractively situated in the central area of the university campus. A statue of Lister Hill and his portrait are displayed prominently on the main floor. In the stacks there are two complete sets of the *Transactions of the Southern Surgical Association.* Two rooms on the upper floor are memorials to physicians who made enduring contributions to this institution and to medicine and surgery nationally and internationally. One of them was Tinsley Harrison, renowned educator in internal medicine. The other was Champ Lyons, active member of the Southern Surgical Association from 1945 until his death in 1965. The Champ Lyons Room is filled with his memorabilia and also contains a Moretti marble bust of W. E. B. Davis, Founder of the Southern Surgical Association.

In addition to its general reference section, the Lister Hill Library houses two important historical collections. One of these, the Reynolds Historical Library, contains rare medical, dental, and scientific texts, manuscripts, and letters accumulated by Dr. Lawrence Reynolds, a noted Alabama bibliophile, and which were given by him to the Medical Center in 1958. The other is the Alabama Museum of the Health Sciences, which contains instruments, photographs, documents, and other pieces of equipment significant in the history of medicine and related fields in Alabama. The desk and books of Luther Hill are displayed in the museum, and there is a large collection relating to J. Marion Sims. There are also individual biographical files on Luther and Lister

Hill, the Davis brothers, and many Alabama physicians, including those who became presidents of the Southern Surgical Association.

State supported institutions such as the University of Alabama, or any other university that falls in the same category, can encounter unexpected severe budgetary restrictions as a consequence of events such as the problems now besetting the oil industry or the Black Monday crisis in the stock market. The State of Texas educational system, for example, perhaps the most heavily endowed in the nation, is currently attempting to cope with substantial reductions in its operational funds. The University of Texas Libraries are obliged to share their part of the problem. Moreover, municipal libraries, such as those of Dallas or Houston, are similarly affected by the economic climate, and have been obliged to reduce their staffs and their acquisitions. When major budgetary restrictions are imposed on libraries, the divisions likely to suffer most are those devoted to the special collections, unless some specific provision has been made for their support. If the University of Alabama at Birmingham were confronted with unusual money problems, it is not to be expected that the Lister Hill Library would give a very high priority to the continuing needs of the Southern Surgical archives. It seemed prudent to the committee, therefore, to investigate the possibility of establishing within the university a permanent endowment fund, the income from which would be expended only for the preservation, maintenance, and utilization of the archival collection.

A plan to achieve this objective was developed as follows. Joseph M. Donald, a highly respected Birmingham surgeon and an active and devoted member of the Southern Surgical Association, was elected to its Presidency in December 1960, but died only 2 months later, on February 13, 1961, before he could serve his term. Joe Donald had made many enduring contributions to medicine and surgery, especially in his own State, and had a wealth of friends and admirers. A proposal was made to Dr. Diethelm that consideration be given to the establishment at UAB of a Joseph M. Donald Memorial Endowment Fund, the sole purpose of which would be to ensure in perpetuity the maintenance and utilization of the Southern Surgical Association historical collection.

Dr. Diethelm responded to this proposal by pledging that the UAB Department of Surgery would contribute $5,000.00 a year to the fund for a minimum of 3 years. The Council of the Southern Surgical Association approved the project and made an initial annual pledge of $1,000.00 to it. On June 17, 1987, the instrument of trust defining the purpose and conditions of the agreement was submitted by President McCallum to the Board of Trustees of the University. The approval of the Board, which was granted on that date, was the final step in establishing the Lister Hill Library as the official archival repository of the Southern Surgical Association.

An initial goal of $50,000.00 was announced in the document. In the 6 months between the announcement and the anniversary meeting of the Southern Surgical Association, this first plateau was reached in donations and pledges. Much of the credit for this gratifying response should be given to Joseph M. Donald, Jr., member of the Association since 1971, and to his wife and family, who have worked diligently to publicize the fund and to encourage contributions to it. Other Birmingham members of the Association have also participated in this effort. The second plateau of the goal for this endowment, but not the last one, will be $100,000.00.

The Southern Surgical Association owes an enduring debt of gratitude to Dr. Diethelm and President McCallum of the UAB and to the Birmingham members of the Association for their cooperation and influence in helping to establish a permanent home for the organizational archive in a location so well suited to this purpose.

The 100th Anniversary Meeting and the Century Ahead

In appreciation of the historic significance of the 100th anniversary meeting, arrangements were made on this occasion, for the first time, for professional videotaping of the opening ceremonies, the presidential address, the Monday morning and Wednesday morning symposia, and portions of the social events. Taping was done under the direction of Mr. Leo T. McGovern, Chief Executive Officer of Ciné-Med Inc., of Woodbury, Connecticut. One complete copy of the videotapes will become a part of the archival collection.

Special features of the opening ceremonies that will become important parts of the videotape collection include a prayer of invocation by Association member, the Reverend Raymond C. Ramage, M.D., and a videotaped message of greeting from the President of the United States, Ronald Reagan, and the First Lady. Before her marriage, Miss Nancy Davis had attended the 1948 meeting of the Association with her parents, Dr. and Mrs. Loyal Davis of Chicago. Dr. Davis had been an active member of the Association from 1933 until his death in 1982.

An additional special feature was the presentation to the Homestead Hotel by the Association of a bronze plaque commemorating the celebration of the 100th anniversary meeting, the 28th meeting of the Association to be held at the Homestead. The plaque was accepted formally by Mr. Daniel H. H. Ingalls, Jr., President of the hotel. It will be mounted on the front veranda in proximity to three commemorative plaques that are already there. Replicas of the plaque, each mounted on a 5 × 7-inch mahogany base, were presented to each member in attendance as a souvenir of the meeting, and will also become a part of the historical collection, along with the design drawings and rubbings of the plaque.

Throughout the anniversary meeting, an elaborate historical exhibit was on view in the South Terrace of the Homestead Hotel. Most of the items comprising the archival collection were displayed, along with special exhibit panels prepared by designated members from each of the Southern states. In 1988, the historical collection will be transferred to its new home in the Lister Hill Library at the University of Alabama in Birmingham.

During the centenary meeting a decision was made by the Council and approved by the membership of the Association to establish the office of Archivist, placing this responsibility on the treasurer, who is also the editor of the annual volume of *Transactions.* This wise decision affirms that as the Association embarks on its second century, its members have recognized the important place that its deliberations occupy in the corpus of surgical history in America, and ensures that the documentation of its proceedings and preservation of its archives will never be overlooked or neglected.

Reference

1. Sabiston DC Jr. Major contributions to surgery from the South. Ann Surg 1975; 181:487–507. (Also in Trans South Surg Assoc 1974; 86:1–21.)

Important Risk Factors of Allograft Survival in Cadaveric Renal Transplantation

A Study of 426 Patients

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Multiple risk factors contribute to the allograft survival of patients who have cadaveric renal transplantation. A retrospective review of 19 such factors in 426 patients identified race, DR match, B + DR match, number of transplants, and preservation time to have a significant influence. The parametric analysis confirmed the effect to be primarily in the early phase, *i.e.*, first 6 months. All patients received cyclosporine with other methods of immunosuppression resulting in an overall 1-year graft survival rate of 66%. The overall 1-year graft survival rate in the white race was 73% and in the black race was 57% (p = 0.002). Allograft survival and DR match showed white recipients with a 1 DR match to have 75% survival at 1 year compared with 57% in the black patient (p = 0.009). If HLA B + DR match was considered, the white recipient allograft survival increased to 76%, 84%, and 88% for 1, 2, and 3 match kidneys by parametric analysis. Patients receiving first grafts had better graft survival (68%) than those undergoing retransplantation (58%) (p = 0.05). Organ preservation less than 12 hours influenced allograft survival with a 78% 1-year survival rate compared with 63% for kidneys with 12–18 hours of preservation. Despite the benefits of B + DR typing, short preservation time, and first transplants to the white recipient, the allograft survival in the black recipient remained uninfluenced by these parameters.

THE IMPROVEMENT IN the results of cadaveric renal transplantation since the advent of the cyclosporine era has been well supported by a number of multicenter and single center reports. The European multicenter trial[1,2] and the Canadian trial[3] reported 1-year allograft survival rates of 72% and 80%, respectively. Opelz[4] reported a 1-year survival rate of 76%, and recently Cicciarelli et al.[5] reviewed data from 3500 transplant patients receiving cadaveric kidneys showing a 75% allograft survival rate at 1 year. Kahan and colleagues[6] reported a 1-year survival rate of 245 cadaveric renal allografts to range from 77% to 85% depending on the method of cyclosporine administration. Despite these encouraging reports, the overall 1-year allograft survival rate in our experience with cyclosporine in various combinations with other drugs was 66% compared with our previous survival rate of 57% in patients receiving azathioprine and prednisone.

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The current study examines the important factors pertaining to allograft survival with special emphasis on the histocompatibility match, race, first and second transplants, duration of preservation, percent reactive antibody, and the presence of diabetes. This single center review has two important features in that all operations were performed by five surgeons and 95% of all kidneys were procured by one organ procurement center with preservation by cold storage using Eurocollins solution. The large number of black patients in this study (41%) allowed a unique opportunity to study the racial effect on graft survival.

Clinical Material and Methods

From December 1983 until January 1, 1986, 437 consecutive patients underwent cadaveric renal transplantation at the University of Alabama Medical Center. This study includes 426 of those patients excluding 11 children younger than 10 years. The immunosuppressive therapy in all patients included cyclosporine, prednisone, and other additional agents such as azathioprine, OKT3 monoclonal antibody, and rabbit antithymocyte globulin (RATG). The RATG was prepared in the Department of Surgery Transplantation Research

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Presented at the 100th Anniversary Meeting of The Southern Surgical Association, Hot Springs, Virginia, December 6–9, 1987.

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TABLE 1. *Overall Allograft Survival**

Months After Operation	Control	All C_sA Groups	C_sA I	C_sA II	C_sA III
	% N	% N	% N	% N	% N
0	100 (100)	100 (426)	100 (80)	100 (84)	100 (262)
3	66 (66)	75 (321)	70 (56)	82 (69)	75 (196)
6	62 (62)	71 (279)	68 (54)	76 (64)	71 (161)
12	57 (57)	66 (195)	60 (48)	71 (60)	67 (87)
24	48 (47)	58 (78)	52 (39)	58 (38)	65 (1)

* p = NS.

Laboratory using 1 × 10^8 human thymocytes injected intravenously into rabbits on day 0, 14, and bleeding on day 21. A crude globulin was then prepared and 4 ml of RATG was administered intravenously for 4–7 days.

The three groups of patients include Group I, which comprised patients who received cyclosporine and prednisone (N = 80). The initial dosage after transplantation was 12-17 mg/kg/day of cyclosporine and 200 mg qd of prednisone. The cyclosporine was tapered to 7–10 mg/kg and the prednisone decreased to 30 mg qd at 30 days. Group II comprised patients who received cyclosporine, RATG, and prednisone (N = 84). The initial dosage of cyclosporine was 5 mg/kg/day, 4 ml/day of RATG for 4–7 days, and 100 mg/day of prednisone. The RATG was discontinued between the 4th and 7th posttransplant day at which time the cyclosporine was increased to 10–14 mg/kg/day and prednisone gradually decreased to 30 mg/day at 30 days after transplantation. Group III comprised patients who received cyclosporine, prednisone, and azathioprine (N = 262). The initial dosage was 5 mg/kg/day of cyclosporine, 2 mg/kg/day of prednisone, and 100 mg/day of azathioprine (see Table 1). The cyclosporine dosage was adjusted according to serum or blood levels and serum creatinine level. Measurements of trough levels included both serum and whole blood using radioimmunoassay (RIA, Sandoz Pharmaceuticals, East Hanover, NJ). The therapeutic range for serum cyclosporine was 100–250 ng/ml and for whole blood was 250–500 ng/ml. The prednisone dosage immediately after operation was gradually reduced to 30 mg/day at 1 month. In most patients the prednisone dosage at 6 months was 15 mg/day or less, and at 1 year was between 10 and 12.5 mg/day. In no patient was prednisone completely withdrawn. The azathioprine dosage of 100–125 mg/day remained constant except for reduction when the white blood count was less than 4,000/mm^3.

TABLE 2. *Renal Disease*

Diabetic	74 (17%)
Glomerulonephritis	93 (22%)
Vascular	91 (21%)
Interstitial	34 (8%)
Hereditary	54 (13%)
Collagen	8 (2%)
Acquired	5 (1%)
Other/Unknown	67 (16%)

The diagnosis of rejection was established by the clinical signs of graft enlargement, fever, and renal tenderness combined with the laboratory evidence of an increase in serum creatinine and blood urea nitrogen levels with evidence of rejection by renal scintigraphy including a decrease in the effective renal plasma flow. Allograft rejection was treated by an increase in oral steroids to 5 mg/kg/day with gradual reduction to 1.5 mg/kg/day 7 days later and to a level of 30 mg/day 10–14 days after the onset of rejection. One gram of intravenous methylprednisone was given daily for the first 3 days of the antirejection treatment. If rejection recurred it was treated a second time with three intravenous pulses of methylprednisone (1 g each) with or without an increase in oral steroids. No patients were treated more than twice for rejection.

OKT3 monoclonal antibody was used for the treatment of acute rejection. This was used instead of corticosteroids in some patients as the primary treatment of acute rejection and also in the management of those patients who failed to respond to steroid therapy as a means of rescue therapy. OKT3 treatment included a dosage of 5 mg/day intravenously for 10–14 days. During OKT3 administration, cyclosporine was reduced to 5 mg/kg or less and azathioprine decreased to 25 mg/day. Prednisone administration continued at 30 mg/day.

All kidneys, procured from heart beating cadavers, were preserved by cold storage using Eurocollins solution and removed from patients pronounced brain dead from the ages of 2–67 years. More than 95% of the kidneys were procured and preserved by the Alabama Regional Organ and Tissue Center and less than 5% were transported to this center from other programs. The age of the recipients ranged from 10 to 66 years with a mean age of 38 years (SD: 11 years). Two hundred and seventy-five patients (65%) were male and 151 patients (35%) were female. Two hundred and fifty-one (59%) were white and 175 were black (41%). The primary disease of the recipient patient is demonstrated in Table 2. The age distribution is depicted in Table 3. All operations were performed by five faculty surgeons of the Department of Surgery with the pre- and postoperative management by the transplant nephrologists and surgeons of the transplant service. All patients after hospital discharge were followed up in the renal transplant clinic in conjuction with the referring nephrologist. None of the 426 patients were lost to follow-up. The minimum follow-up for functioning allografts was 3 months, the maximum was 38 months with a mean graft time of function of 12.8 months (SD: 10.5 months).

The control group included the 100 patients receiving cadaveric kidneys before December 1983, preserved by Eurocollins solution. These patients received azathioprine and prednisone as immunosuppressive therapy and were analyzed for allograft survival 1 year after transplantation. The initial dosage of azathioprine was 100–150 mg qd with long-term maintenance at 100–125 mg qd. The initial prednisone dosage of 5 mg/kg/day was reduced to 30 mg/day at 1 month. Rejection was treated with three pulses of intravenous methylprednisone over 3 days frequently combined with an increase in oral prednisone.

In Groups I and II the cyclosporine dosage was given orally each morning in almost all patients and adjustments were made to maintain serum trough levels at 24 hours between 50 and 200 ng/ml. In Group III the same dosage schedule was maintained with whole blood levels between 250 and 500 ng/ml. Intravenous cyclosporine was rarely used except where oral intake was not possible. In such circumstances the intravenous dosage was one third of the oral dosage.

Histocompatibility matching with HLA typing was performed in all patients receiving cyclosporine. DR matching was completed in all but 22 patients. Those patients receiving azathioprine and prednisone in the control series had complete HLA typing but incomplete DR typing. Blank donor/recipient antigens were not counted as a match when calculating the number of matched HLA − A, B or DR antigens. Percent reactive antibody (PRA) levels were calculated from serum lymphocyte cytotoxicity assays against a 42-member sera-defined frozen sera panel. The final crossmatch between the patient and donor consisted of three separate assays, which included an Amos modified wash assay, a three wash procedure, and extended incubation crossmatch. Mixed lymphocytes were used in all assays. A B lymphocyte crossmatch was performed if the extended incubation indicated possible B cell antibodies.

After all data were verified, actuarial analysis of survival was accomplished by the Kaplan-Meier method,[7] with the Gehan-Wilcoxon[8] technique providing the p value for stratified curve comparison. A hazard function (the instantaneous risk in patients not yet experiencing graft loss) for loss as a time related event was determined by the parametric model of Blackstone, Naftel, and Turner.[9] The model identified an early (0–6 months) and constant phase (6 months +) and determined the incremental risk factors for graft loss for each phase. The constant phase begins at time zero. Its effect becomes relatively important after the early phase diminishes at about 6 months. Variables were considered important only if their p value was less than 0.06. All confidence limits were expressed as 70%. Graft loss was considered to be at the time of nephrectomy, return to dialysis or death if the graft was functioning. There were no exclusions for technical or nonimmunological failures.

TABLE 3. *Age in Years*

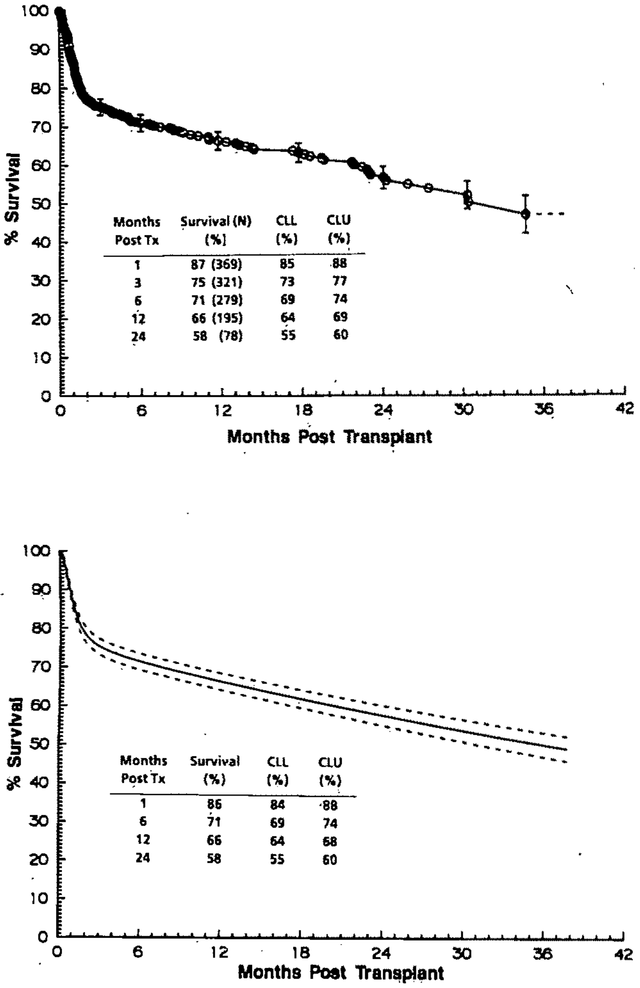
10–19	26 (6%)
20–29	72 (17%)
30–39	127 (30%)
40–49	148 (35%)
50–59	46 (11%)
60+	7 (1%)

Nineteen potential risk factors were examined in the parametric model including age, sex, race, total number of transplants, A match, B match, A + B match, DR match, B + DR match, peak PRA, current PRA, sensitized PRA if peak or current is greater than 10%, past positive but current negative (PPCN) PRA, previous transplant antigen mismatch, type of renal disease, donor race, donor sex, donor age, and total preservation time of the allograft. In addition, these risk factors were analyzed for possible interactions. An accurate history of previous blood transfusions was not available and therefore not included in the analysis. However, the policy of deliberate blood transfusions before transplantation as a means to induce a transfusion effect was discontinued before December 1983.

Results

Allograft Survival

The overall graft survival of all patients receiving various immunosuppressive protocols including cyclosporine was compared with the control group of patients receiving azathioprine and prednisone and revealed the 12-month graft survival rate of the control group to be 57% compared with 66% of the cyclosporine group (p = 0.08) (see Table 1). Three subgroups comprised 426 patients in the cyclosporine group. Group I (N = 80) included cyclosporine and prednisone. Group II (N = 84) included cyclosporine, prednisone, and RATG. Group III (N = 262) included cyclosporine, prednisone, and azathioprine. The 12-month graft survival rates of the three subgroups were 60%, 71%, and 67%, respectively (p = NS). The overall graft survival rate of patients receiving cyclosporine was 66% at 1 year, shown in Fig-



Months Post Tx	Survival (N) (%)	CLL (%)	CLU (%)
1	87 (369)	85	88
3	75 (321)	73	77
6	71 (279)	69	74
12	66 (195)	64	69
24	58 (78)	55	60

Months Post Tx	Survival (%)	CLL (%)	CLU (%)
1	86	84	88
6	71	69	74
12	66	64	68
24	58	55	60

FIG. 1. Allograft survival in 426 patients receiving cadaveric kidneys is demonstrated by the Kaplan-Meier analysis in the upper figure (1A) with the expressed upper (CLU) and lower (CLL) 70% confidence limits (confidence limits in brackets). The lower figure (1B) is the predicted survival based on the parametric analysis when no risk factors are considered (confidence limits in dotted lines).

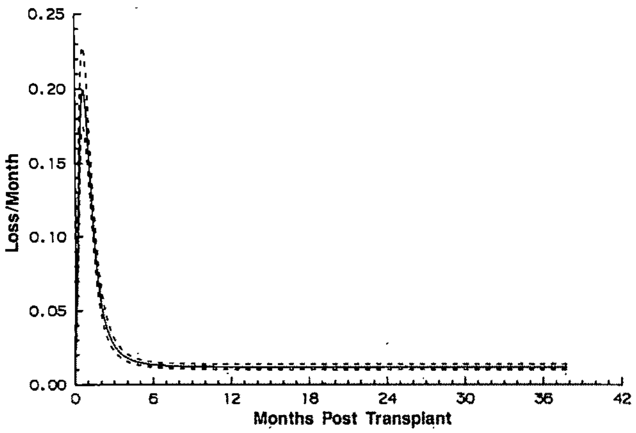


FIG. 2. Early allograft loss is depicted in both the early (first 6 months) and the late (subsequent 32 months) phase when no risk factors are considered (parametric).

TABLE 4. *Potential Risk Factors*

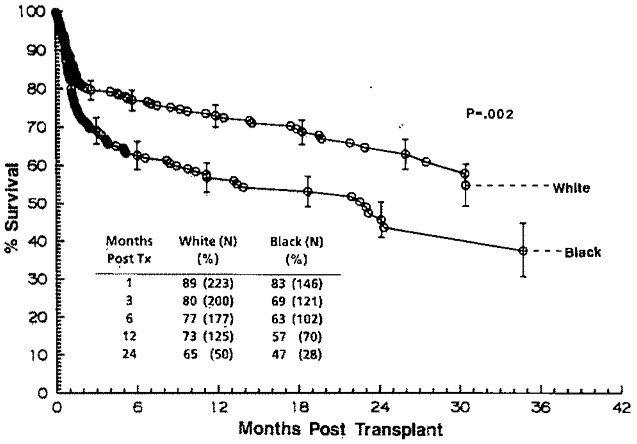
Age
Sex
Race
No. of transplants
A match
B match
A + B match
DR match
B + DR match
Preservation time
Peak PRA
Current PRA
PRA 10%
PPCN PRA
Previous Ag mismatch
Renal disease
Donor age
Donor race
Donor sex

PRA = Percent Reactive Antibody
PPCN = Percent Positive Current Negative

ure 1, decreased to 58% at 2 years (Kaplan-Meier). This survival curve compared closely with the projected survival by the parametric analysis (Fig. 1). The parametric analysis presented in Figure 2 emphasized the early high instantaneous hazard to allograft survival in the early phase (*i.e.*, the first 6 post-transplant months). This was followed by a remarkably low graft loss during the constant phase (the next 32 months).

The important risks determined by multivariate analysis of nineteen factors revealed five to be important (see Table 4). These were the recipient race, number of transplants performed, DR match, B + DR match, and organ preservation time. These risk factors had a significant and relevant effect on allograft survival.

The comparison of allograft survival in recipients of the black race (N = 175) versus those of the white race (N = 251) receiving cyclosporine, compared in Figure 3, showed the white recipient to have a 73% 1-year allograft survival rate versus the 57% survival rate of the black recipient (Kaplan-Meier) (p = 0.002). The parametric analysis in Figure 4 showed both races to have a high risk for allograft loss in the early phase. However, black patients have a risk of graft loss greater than white



Months Post Tx	White (N) (%)	Black (N) (%)
1	89 (223)	83 (146)
3	80 (200)	69 (121)
6	77 (177)	63 (102)
12	73 (125)	57 (70)
24	65 (50)	47 (28)

FIG. 3. Comparison of allograft survival between black and white recipients demonstrates improved allograft survival in white recipients (Kaplan-Meier).

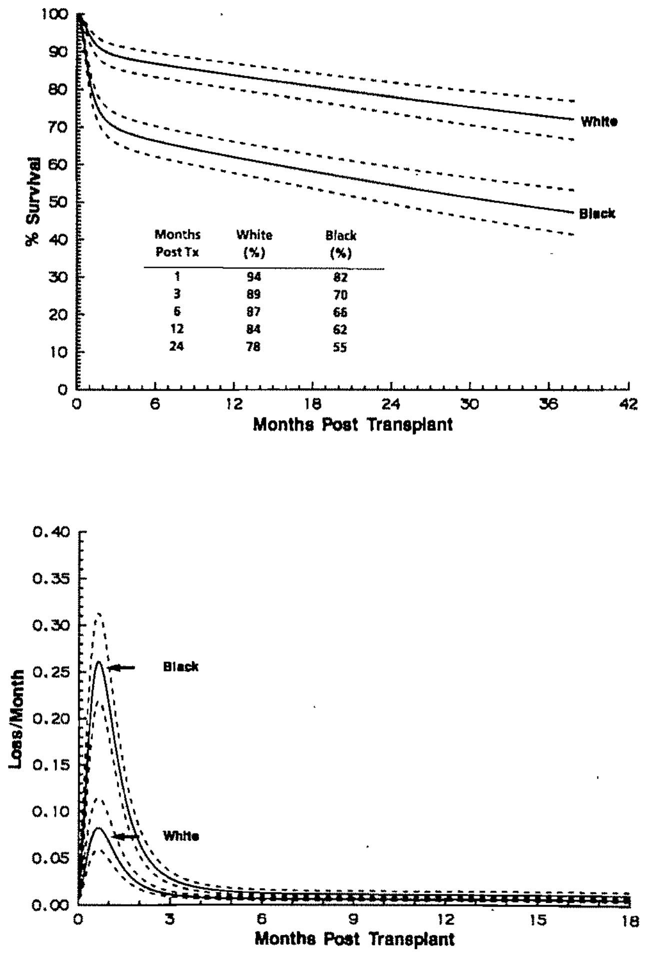


FIG. 4. The lower figure shows renal allograft loss in both races to occur in the early phase in the post-transplant course with the risk of allograft loss greater in blacks. The constant phase from 6 to 18 months shows blacks to continue to have a greater allograft loss. The upper figure compares renal allograft survival in the two races. For both figures, the equation was solved for: total number of tx = 1, for whites B + DR = 2, peak PRA = 0, ischemic preservation time = 12 hours (parametric).

recipients in both the early and constant phase. The racial origin of the donor kidney had no significant effect on allograft survival. (White donor to white recipient [N = 232] *vs.* black donor to white recipients [N = 19] or white donor to black recipient [N = 148] *vs.* black donor to black recipient [N = 27].)

Allograft Survival and DR Match

Allograft survival in all patients with 0, 1, and 2 DR matches are compared in Table 5. At 1 year, patients with a zero DR match had a 63% graft survival rate (N = 225), a one DR match had a 68% graft survival rate (N = 165), and a two DR match had an 84% graft survival rate (N = 14). Separation of the patients by race and DR match showed the white recipients to have a 75% survival rate at 1 year compared with a 57% survival rate in the black recipient patients receiving a one DR match graft (p > 0.009) (Fig. 5) (Kaplan-Meier).

TABLE 5. *Allograft Survival and DR Match*

Months After Operation	0 DR % N	1 DR % N	2 DR % N
0	100 (225)	100 (165)	100 (14)
3	71 (160)	78 (128)	93 (13)
6	67 (136)	74 (112)	93 (13)
12	63 (91)	68 (82)	84 (7)
24	51 (36)	64 (29)	84 (1)

0 DR vs. 1 DR p = 0.09
0 DR vs. 2 DR p = 0.04
1 DR vs. 2 DR p = 0.12

Allograft Survival and HLA B + DR Match

When HLA B match and DR match were combined (B + DR), important differences were noted in overall allograft survival between the 0, 1, 2, and 3 matched kidneys. The 0 match kidney had a 58% 1-year survival rate compared with 70%, 73%, and 82% survival rates for 1, 2, and 3 B + DR matched grafts (p = 0.03, 0.009 and 0.06, respectively) (see Table 6). The parametric analysis depicted in Figure 6 showed the risk of early graft loss confirming the beneficial effects of B + DR typing in white recipients similar to that noted in the Kaplan-Meier analysis of Figure 5. Black patients exhibited the same allograft survival regardless of the B + DR matching.

Allograft Survival, B + DR Match and Racial Consideration

If racial influence was considered with the B + DR match, an important difference was noted in the para-

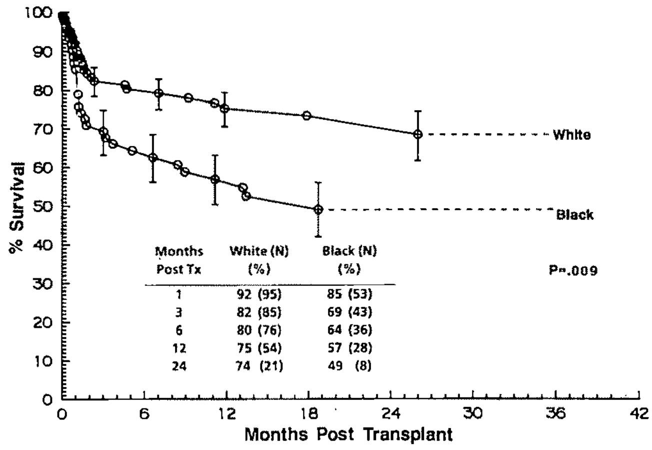


FIG. 5. Allograft survival in black and white patients with a 1 DR match shows the white patients to have a 75% 1-year graft function compared with 57% in the black recipient (p = 0.009) (Kaplan-Meier).

TABLE 6. *Allograft Survival and B + DR Match*

Months After Operation	0 B + DR	1 B + DR	2 B + DR	3 B + DR
0	100 (160)	100 (166)	100 (63)	100 (14)
3	67 (107)	78 (129)	82 (52)	93 (13)
6	63 (88)	73 (113)	82 (47)	93 (13)
12	58 (54)	70 (85)	73 (34)	82 (7)
24	52 (25)	56 (27)	69 (12)	82 (2)

0 B + DR vs. 1 B + DR p = 0.03
0 B + DR vs. 2 B + DR p = 0.009
0 B + DR vs. 3 + 4 B + DR p = 0.06
1 B + DR vs. 2 B + DR p = 0.28
1 B + DR vs. 3 + 4 B + DR p = 0.26
2 B + DR vs. 3 + 4 B + DR p = 0.60

metric analysis of overall allograft survival between white and black patients (p = 0.003) (Fig. 7). There was no difference in the 3-month allograft loss between black recipients and white recipients with a 0 B + DR match. However, a significant difference was observed in white recipients of a 1 and 2 B + DR match (p = 0.02, p = 0.01, respectively). The allograft hazard loss is depicted by the parametric analysis in Figure 6. Black recipients were at greater risk for allograft loss not only in the early phase (first 6 months after transplantation) but continued throughout the constant phase (32-month follow-up period) (p = 0.05). Figure 6 showed the hazard of allograft loss to exist in the early phase in both races, but the persistent loss was greater in the constant phase of black patients. The individuals at lowest risk in the early phase were those white patients receiving allografts with well-matched B + DR kidneys.

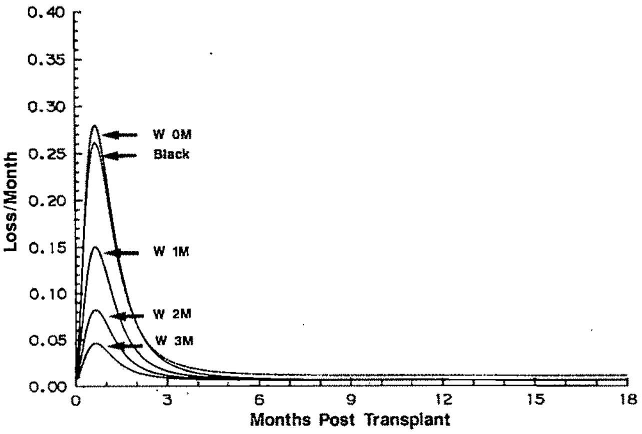
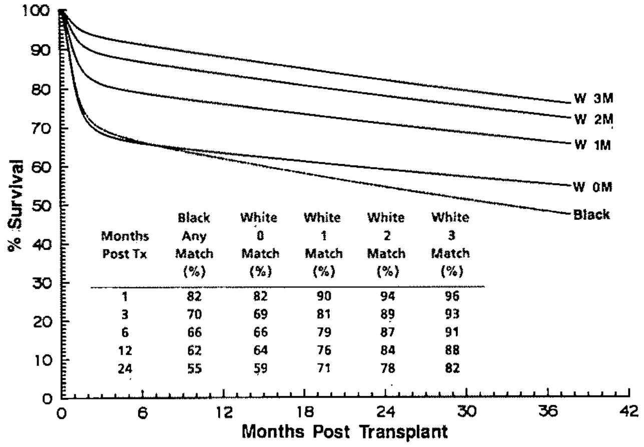


FIG. 6. The hazard of allograft loss in the early and late phases by B + DR match and race shown above, emphasizes the greatest risk of loss to be in the early phase (first 6 months) with little difference in the constant phase (6–18 months). The equation was solved for: total number of tx = 1, total preservation time = 12 hours, peak PRA = 0 (parametric).



Months Post Tx	Black Any Match (%)	White 0 Match (%)	White 1 Match (%)	White 2 Match (%)	White 3 Match (%)
1	82	82	90	94	96
3	70	69	81	89	93
6	66	66	79	87	91
12	62	64	76	84	88
24	55	59	71	78	82

FIG. 7. The effect of combining B + DR match by race, demonstrated above, shows the white patient with the best matched kidneys to have improved allograft survival to the 0 match white recipient or any black recipient regardless of match. The equation was solved for: total number of tx = 1, ischemic preservation time = 12 hours, peak PRA = 0 (parametric).

Allograft Survival in Primary and Retransplantation with Racial and B + DR Consideration

Three hundred and seventy-one patients received first allografts with a 68% 1-year graft survival rate compared with a 58% 1-year graft survival rate of 55 patients undergoing retransplantation (p = 0.05). If the racial influence is taken into consideration in regards to first and second kidney transplants, the white recipient of a first transplant regardless of match (N = 213) had a 76% 1-year graft survival rate compared with a 59% 1-year graft survival rate in a white patient receiving a second or third kidney (N = 38) (p = 0.02). However, in the black recipient with a first transplant (N = 158), there was no significant difference in the allograft survival rate in the first year (57%) compared with the black recipient of subsequent transplants (59%) (N = 17). White patients receiving first transplants (N = 125) had an allograft survival rate of 82% at 1 year in both 1 and 2 B + DR matched groups compared with a 65% survival rate in the 0 B + DR match (N = 66) (p = 0.02 and 0.006, respectively).

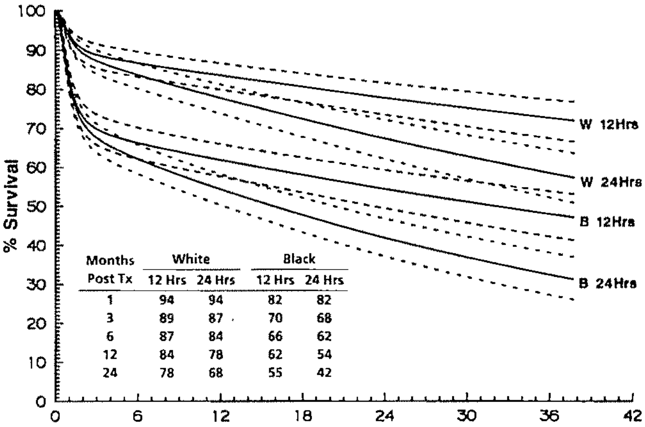
Allograft Survival and Duration of Preservation

Recipients of kidneys (both blacks and whites) preserved by Eurocollins cold storage for less than 12 hours

TABLE 7. *Risk Factors Kaplan-Meier*

Cyclosporine improves graft survival	(p = 0.08)
Primary transplants have better survival	(p = 0.05)
Survival better in white race	(p = 0.002)
B + DR important in white race	(p = 0.02)
Preservation time 12 hours or less	(p = 0.04)

(N = 52) had a 78% 1-year graft survival rate compared with 63% for kidneys preserved 12–18 hours (N = 176) (p = 0.04). Figure 8 predicted the effects of 12 and 24 hours of preservation time on graft survival by parametric analysis emphasizing the improved allograft survival in those patients receiving kidneys preserved for 12 hours or less. Again the racial influence was noted with the black recipients having less favorable survival. Figure 9 showed the allograft loss to be predominantly in the early phase (first 6 months) in both races. Although the allograft survival in the two races was different, the influence of the ischemic interval became increasingly important in the constant phase (p = 0.015). The overall incidence of renal dysfunction after transplantation requiring dialysis in the cyclosporine-treated recipients was 31%. Permanent nonfunction of kidneys after transplantation was 4%.



Months Post Tx	White 12 Hrs	White 24 Hrs	Black 12 Hrs	Black 24 Hrs
1	94	94	82	82
3	89	87	70	68
6	87	84	66	62
12	84	78	62	54
24	78	68	55	42

FIG. 8. A comparison of the preservation interval and allograft survival in blacks and whites is depicted above showing 12 or 24 hours of preservation time in white recipients has a better prognosis for long-term kidney function than black recipients. The equation was solved for: total number of tx = 1, B + DR match = 2, peak PRA = 0 (parametric).

Allograft Survival and the Effect of Percent Reactive Antibody

In the absence of percent reactive antibody, a primary transplant (N = 321) had better graft survival than a retransplant (N = 23) (p = 0.002). This relationship remains consistent if the antibody titer was greater than zero, with patients receiving first kidneys having a 70% 1-year graft survival rate compared with a 56% survival rate (N = 32) if they had one or more previous transplants (p = 0.05).

Allograft Survival and Primary Disease

There was no relationship between the primary renal disease and allograft survival. Because of the increasing number of patients with diabetes, this group was examined. Seventy-four patients with diabetes had a 77% 1-year graft survival rate compared with a 64% graft survival rate in the nondiabetic patient (p = NS). However, when racial influence was considered there was improvement for white nondiabetic recipients (N = 194) as compared with the black recipient patient group (N = 158) (71% *vs.* 56%, respectively) (p = 0.01). When the diabetic black (N = 17) or white (N = 57) patients were compared, there was no significant difference between the two groups. (Note: the N for the black diabetic patient was only 5 at 1 year follow-up compared with 31 in the white diabetic patient).

Mortality

Thirty-five of the 426 patients died within 0–38 months after transplantation. Patients who died with functioning grafts or who died within 3 months of graft failure while on dialysis were included as a mortality. Twenty deaths occurred within the first 3 post-transplant months and 6 occurred between the fourth and twelfth post-transplant month for a 1-year mortality rate of 6%. There were nine deaths after the first year for an overall mortality rate of 8%. Eighteen deaths occurred in white recipients and 17 occurred in black recipients. Twenty-three deaths were in male patients and 12 were in female patients. Twenty-one patients died with functioning kidneys and 14 patients died with nonfunctioning kidneys. Fifteen deaths occurred in patients with diabetes, seven of whom had Type I diabetes. The most common cause of death was infection (10 patients), cardiac (5 patients), CVA (4 patients), gastrointestinal bleeding (4 patients), liver failure (3 patients), pancreatitis (3 patients), carcinoma (1 patient), sickle cell disease

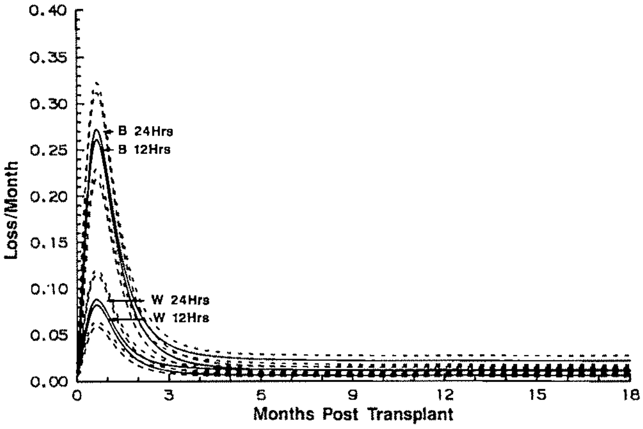


FIG. 9. A comparison of the preservation interval and allograft loss in blacks and whites shows both races to have the greatest risk for graft loss to be in the early phase. The black recipient not only has a greater risk of allograft loss in the early phase, but this continues in the constant phase. The equation was solved for: total number of tx = 1, B + DR match = 2, peak PRA = 0 (parametric).

(1 patient), suicide (1 patient), aortic thrombosis (1 patient), and unknown causes (2 patients).

Discussion

Multiple factors relating to patient death, technical considerations pertaining to nonimmunological causes for allograft loss, and the immunologic events leading to rejection of the kidney play important roles in the success or failure of long-term survival of the transplanted organ (Table 7). The Kaplan-Meier nonparametric analysis (Fig. 1A) demonstrates graft loss in this series of 426 patients to occur most rapidly in the first 3 months after transplant and then to assume a slowly declining graft survival during the next 32 months. The use of a parametric system allows the opportunity to construct a model of time-related distribution of events with specific risk factors for the early, constant, or late phase (Fig. 1B). Thus, the hazard function, *i.e.*, risk of graft loss—for whatever cause—is a time-related event that is influenced by multiple factors. The parametric analysis in Figure 2 shows the graft loss to be greatest in the early phase (6 months) with minimal loss in the constant phase (from 6 to 38 months). If, however, the patients were followed for 20 years, a late phase of graft loss would occur as a result of chronic rejection, which would then progress to renal failure. Blackstone et al.[9] reported a parametric system that allowed the modeling of time-related distribution of those events pertaining to the risk factors of death and other time-related events (graft loss) based on the decomposition of time varying risk factors into a small number of phases. Certain events are specific for each phase (*i.e.*, acute rejection—early phase and chronic rejection for the constant or late phase). Therefore, the hazard or risk function, survivorship function, and probability estimates with confidence limits (70%) are shown using the parametric model (Figs. 1B and 2). This model allows one to examine the relation between risk factors involving graft loss and time-related events, which allows the physician or surgeon involved in patient care the opportunity to develop useful inferences and project the probability of graft survival. This concept is of particular importance in allowing a given transplant program to examine the so called "center effect" as it pertains to the results of allograft survival and allows one to dissect the relevant and significant factors.

A comparison of the parametric model with the Kaplan-Meier graft shown in Figures 1A and 1B confirmed the two curves to be similar. The parametric model of Figure 2 emphasizes the hazard of allograft loss to be greatest in the early phase (first 6 months) followed by a constant phase.

The importance of HLA A and B typing in selecting recipients for cadaveric kidneys has long been a subject of dispute regarding its value in improving allograft survival when recipient patients are treated with azathioprine and prednisone. In 1981, McDonald et al. published a prospective multicenter study of 942 cadaver first allografts which showed HLA A and B typing to be important factors in both early and late allograft survival.[10] Subsequently, data from a similar prospective study[11] of 3811 cadaveric allografts evaluated the impact of HLA A and B typing and also showed allograft to be better in recipients of matched kidneys at 6 months and 4 years after transplantation. The importance of DR typing also has been documented to be of benefit in prolonging graft survival, especially in patients with 2 DR matches.[4,12] Opelz emphasized the beneficial effects of DR typing with cyclosporine as compared with the precyclosporine era.

The effect of HLA A and B matching combined with DR matching on kidney allograft survival in patients treated with or without cyclosporine has also been a matter of controversy. In 1985, Opelz[4] reported for the Collaborative Transplant Study on 2198 recipients receiving first cadaver kidneys to have a 76% 1-year graft survival rate with cyclosporine. This survival rate improved when HLA B + DR matching was combined, and if the recipients had 0 HLA B + DR mismatches, the allograft survival rate increased to 86%. Thus, combining cyclosporine and a kidney with 0, 1, or 2 HLA B + DR mismatches resulted in better allograft survival. These results were similar to those reported by Cicciarelli et al.[5] Both studies support the improved allograft survival noted in this series where recipients of B + 1 or 2 DR matched kidneys had a 73% and 82% survival rate, respectively (see Table 6). Therefore, optimum results appear to occur with the combination of a well-matched HLA B + DR matched kidney and the use of cyclosporine. It is important to emphasize the importance of the combined effect of HLA B + DR matching as opposed to HLA A and B or HLA DR alone. The obvious disadvantages of selecting patients according to tissue typing alone pertain to the large pool of recipient patients needed and the inherent problems of organ sharing and preservation. If, however, all of such factors could be controlled, then the effect of matching with current immunosuppressive drugs becomes important in obtaining optimal results in transplantation.

The effect of race on early and late allograft survival was not apparent in the precyclosporine data analysis from this center when both races had similar results at 1 year.[13] The early reports[14,15] suggesting that blacks had a less favorable allograft survival were reported at a time that DR typing was incomplete. In this report, white patients at 24 months had an allograft survival rate of 65% compared with the 47% rate in the black patients ($p = 0.002$) (see Fig. 3). This discrepancy increased when the cadaveric kidneys were matched with 1 DR grafts ($p = 0.009$), in which case the white recipients had a 7?%

1-year graft survival rate and a 2-year survival rate of 74% compared with 57% and 49% in the black recipients (see Fig. 5). The parametric analysis further elaborates on the effect in Figure 7 showing two and three match kidneys in white recipients to have an 84% and 38% 1-year graft survival rate, respectively (see Fig. 7). Opelz et al. in 1977[14] reported for the first time the apparent negative influence of the black race on allograft survival. This observation raised the important question of whether or not race-specific histocompatibility antigens exist, which might account for the less favorable allograft survival in black patients. The current report supports the observation that black patients have a less favorable graft survival. Black patients and white patients with a 0 match kidney have similar graft survival. However, when kidneys are matched for B + DR in both races, the white recipient has an improved graft survival. Therefore, the positive benefit of tissue typing in white recipients was not apparent in black recipients. The hazards of allograft loss due to acute rejection are especially visible in both races in the early phase (see Fig. 4) and the hazard of graft loss remains greater in the constant phase for the black recipient (see Fig. 4). This suggests that if racial antigenic differences are present, their effects in precipitating graft rejection are a greater risk in the early phase. If the allograft is not subjected to early loss in the black recipient, then the hazards of graft loss in the constant phase remain greater than for the white recipient. The reasons for failure of B + DR matching to improve allograft survival in the black race remain unclear. However, because the effect is most obvious in the early phase, noncompliance or socioeconomic factors are an unlikely cause. Unfortunately, the improved results reported by others of allograft survival in blacks treated with cyclosporine were not confirmed by this report.[16]

There is general agreement that primary or first renal transplants have a better prognosis than second or subsequent allografts.[17] This is particulary important in that the cyclosporine benefit to first graft recipients is not apparent in those patients receiving second or third kidney transplants. This observation was also supported by this study where the overall primary kidney transplant survival rate was 68% compared with a retransplant survival rate of 58% (p = 00.05). This comparison was accentuated in the white patient where the allograft survival rate after primary renal transplantation is increased to 76% (p = 0.02). The black recipient did not show improved allograft survival with the first kidney and maintained a 59% graft survival rate with retransplantation. This is in contrast to the white recipient of a first kidney with a one or two B + DR match where an 82% 1-year graft survival rate occurred. Unfortunately, the black recipient did not share the advantage of a primary kidney with a B + DR match. These results suggest that particular efforts must be directed to the regraft patient in regards to the selection of the donor kidney, to the previous antigens mismatched, duration of preservation, the degree of sensitization, and past positive, current negative cytotoxic antibodies.

There was no obvious effect of the primary renal disease on allograft survival. The hazards of diabetes surprisingly did not appear to be a factor in allograft survival in either the early or constant phase. However, the racial influence was persistent and the white diabetic recipient continued to show improved allograft survival compared to the black patient with diabetes. The importance of pre-existing percent reactive antibody in regards to allograft survival is unclear when the final crossmatch is negative. Some reports have suggested that patients with a high reactive antibody titer have less favorable survival.[18] The results from this study indicate that those individuals with peak antibody titers greater than zero could have better graft survival than those receiving previous transplants. Thus, preoperative sensitization did not seem to have an adverse impact on long-term graft survival if the preoperative crossmatch was negative. It is accepted, however, that early postoperative renal dysfunction may be due to immunologic factors such as subclinically detectable antibody titers, which may be responsible for accelerated type of rejections.[19] This study did not examine this question in greater detail than the allograft survival in relation to antibody titer.

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DISCUSSION

DR. JOHN C. MCDONALD (Shreveport, Louisiana): This is a careful and important presentation from the University of Alabama cadaver renal transplantation. It makes several important points that are quite significant, and I commend Dr. Diethelm and his associates for this scholarly work.

Because of limited time, my comments are directed to one issue, which is the importance of tissue matching.

Under Dr. Diethelm's leadership, the University of Alabama's renal transplant program has become the second or third busiest such program in the nation. They perform about 150 grafts per year, which places them somewhat behind the University of California at San Francisco and about even with the University of Minnesota and the University of Pittsburgh, and certainly makes them the highest volume center in the South.

I have observed that all high volume centers have certain common characteristics. They have an enormous patient waiting list. They have a highly effective organ procurement program. They are generally committed to the concept that short preservation times are more influential in the outcome than tissue matching.

These characteristics lead them to perform many transplants that are poorly matched and very few that are well matched. Thus, when they analyze data, they generally see little influence of matching because they have what is really an insignificant number of well matched grafts.

I was quite surprised to see a significant influence of matching in this series, since there are only 14 reasonably well matched patients in the series of 403. It is clearly not unexpected that no relationship between matching and outcome was observed in the 175 black recipients, since there could have been only a handful of reasonably matched patients in this group.

Therefore, while it is perfectly correct to say that a black patient receiving a totally mismatched graft has a smaller chance of success than a Caucasian patient receiving such a graft, and similarly, that a one antigen matched graft is more likely to fail in a black patient than in a Caucasian patient, it is not possible to make a statement regarding the importance of matching in the black group from the data provided.

I would appreciate hearing from Dr. Diethelm's discussion of this issue and would pose two further questions:

Why did he not consider the A locus in his analysis, since most students of the field attribute a similar influence to the A, B, and D-R loci, and finally, has his finding of a favorable effect of matching in this highly mismatched group of patients led him to modify his clinical protocols regarding matching?

DR. ROBERT E. RICHIE (Nashville, Tennessee): I would like to congratulate the authors for bringing to us a superb analysis of the numerous variables which are involved in the success or failure of the renal allograft.

During the last two decades we have seen the one-year cadaver allograft survival improve from 45% to the present level of 85 to 90%. In my opinion, the strength of this paper lies in the complexity with which these many variables were examined.

Historically, small clusters of variables have been analyzed and may not, in fact, have given us the scope that we needed.

Another major contribution of this paper is the vast experience with transplantation in the black population. At our institution we have seen our 1-year functional graft survival improve from 68% in 1984, (at a time when only a few patients received cyclosporine, namely, those patients who could afford it), to 89% this past year when every patient received cyclosporine.

During the same time, the one-year patient mortality dropped from 5.2% in 1984 to 1.3% in 1986.

I am envious of Dr. Diethelm. He reports that greater than 90% of the cadaver kidneys transplanted are locally procured. In our program, 50% of the cadaver transplants are procured from other centers.

Local procurement has the usual advantage of decreased preservation time and better quality assurance. Dr. Diethelm did not mention acute tubular necrosis in his study. I would like to have him comment on the incidence of this and the implications relative to the time when cyclosporine was started.

The other point I would like to have him comment on is: Does he feel that the use of cyclosporine overcomes the so-called transfusion effect, since his manuscript states they no longer deliberately transfuse patients prior to transplantation?

DR. JOHN D. WHELCHEL (Atlanta, Georgia): I, too, would like to take this opportunity to compliment Dr. Diethelm and his colleagues on the excellent piece of work in this paper.

For years, we in the South have been looking at the results coming out of the Northwest that we couldn't reduplicate, and we always wondered why. Maybe we thought we were a little inferior. But I think Dr. Diethelm's work today gives us a good idea of some of the factors that may relate to the discrepancy we see coming from the Northwest and Midwest compared to things that we have been able to accomplish in the South.

I would like to ask Dr. Diethelm to comment on the fact that in most of the situations in transplant programs, we see that the results of living-related donor transplants in the black and white population is very similar, if not identical. Why then do we see this discrepancy in the cadaveric list and the cadaveric recipient?

I personally think it has a lot more to do with typing, but I would like Dr. Diethelm's own experience and his thoughts concerning this problem.

DR. THOMAS PETERS (Memphis, Tennessee): (Slide) Dr. Diethelm, your nicely presented data are of great interest and relate to important aspects of organ procurement and use across the country today.

The Southeastern Organ Procurement Foundation (SEOPF) data base has recently been examined regarding the same questions that you raise.

In a series of 3798 cadaveric kidney transplants from 52 SEOPF institutions, similar risk factors to the 27 studied at the University of Alabama were reviewed. Interestingly, 1411 kidneys came from multiorgan donors, while 2387 were from kidney-only donors. We also used univariate and multivariate techniques to determine early and late risks to allograft function.

We found, first, that multiorgan donation did not influence outcome for the kidney allograft recipient. In agreement with data in your abstract, we found that risk to graft was significant with the patient receiving a second or subsequent transplant. Also, peak panel reactive antibody greater than 60%, poor match at the HLA-AB and DR loci, as well as delayed graft function adversely influenced outcome. In these points, SEOPF data agrees with that from Birmingham. We also found that recipient race (white) was significantly favorable to outcome and that recipient age did not relate to outcome.

Of particular note, sharing *per se*, or shipment of kidneys had no effect on graft outcome, early or late.

My question, then, relates to the data regarding risks to graft loss in your study, confirmed by multicenter SEOPF data: What can the transplant surgical community do to limit these risks? It seems that organ-sharing based upon matching, especially for the multiply transplanted or sensitized recipient, would be helpful. Do you think that organ-sharing based upon immunologic criteria should, therefore, be expanded?

DR. A. G. DIETHELM (Closing Discussion): I would like to thank Dr. McDonald, Dr. Richie, Dr. Whelchel and Dr. Peters for their comments.

Dr. McDonald raised the important question that we had very few well matched patients of the black race, and it might be difficult to draw a conclusion from these few numbers. That is true, and it is also part of the dilemma. It is very difficult to obtain a good match in the black recipient. I will come back to that in a minute.

Concerning the question of the A locus: We did look at that question, but we found that the B plus DR-locus gave us the best benefit. This is not a unique observation with us. Dr. Terasaki's group has published that same observation some two years ago.

As regards the question of whether or not it will change our patient selection: It has, and I think that there are two observations that I would like to mention that are important at the present time. One is that we were clearly limited with cold storage hypothermic preservation, and we had a 28% dialysis requirement with an average cold storage time of 17 hours.

We switched to the Belzer perfusate and used pump perfusion, and now we have an average of a 30-hour ischemic preservation time with a 2% dialysis requirement for ATN. This particular change has made an important difference and will be important in the future in the selection of patients according to typing.

In our institution, it would not be possible to achieve better results by improved typing with the current limitations of the cold storage Eurocollins solution.

Dr. Belzer has a new solution that will be started in the multicenter trial and might be even more beneficial than the current techniques.

Dr. Richie asked about the incidence of ATN. I just mentioned that 28% of patients with an average preservation time of cold storage for 17 hours with Eurocollins solution did have important ATN.

We have tried a number of protocols with cyclosporine in this study. The best protocol was to start with either 5 mgs per kg per day of cyclosporine or less. We combine this with some form of antithymocyte globulin or OKT3 monoclonal antibody and do not increase the cyclosporine until the serum creatinine is 3 mgs or less.

The question of cyclosporine and blood transfusions poses some difficulties. It has been known for a number of years that patients receiving multiple transfusions have better cadaveric graft survival. The combined effect of cyclosporine and blood transfusion in our experience is minimal. I think one would have to look at Opelz's data from Europe, and there may be a positive effect with transfusions when combined with cyclosporine.

Dr. Whelchel asked the question of what can be done to better look at the antigenic profile of black patients.

First of all, we do need to have better techniques so that we can type for all antigens. At the present time we often have one, two or three antigens correctly typed in the black race, so, obviously, accurate tissue typing is not possible. This will require not only increased effort and time, but new techniques.

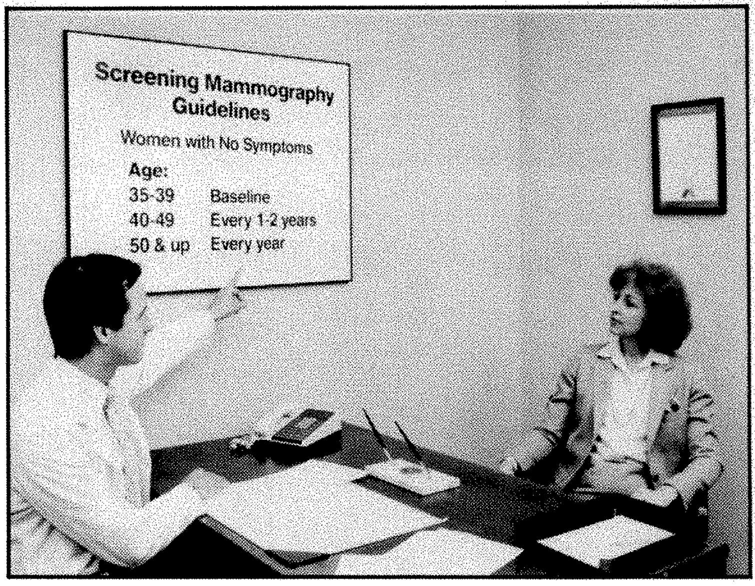
Dr. Peters asked what could be done to improve organ sharing and whether I believe that organ sharing should be carried out on an immunologic basis regarding the best match available.

I do believe that the data we have seen today and the information that has been published by Dr. John McDonald from SEOPF as well as information from Dr. Paul Terasaki in California all suggest that better matched patients may do better in the long run regarding graft survival. This is assuming that certain variables remain constant, and the most important variables that pertain to graft survival are those that occur in the first three months.

The best and most effective immunosuppressive therapy must be utilized. Yet there will still be certain patients, particularly those who are black, who proceed to reject their kidneys, despite maximal available immunosuppressive therapy. So in response to Dr. Peters, I will say that I am certainly not opposed to organ sharing as long as the important variable of organ ischemia is acceptable. We have to limit the duration of preservation to that time which is appropriate with organ viability and prompt function.

Last comment: For a number of years there has been a great deal of discussion about the center effect in transplantation. This is probably the same in all of surgery. Some hospitals, some surgeons and some transplant centers have better results, whereas others have less good results. This study, however, was the first opportunity we have had to use the parametric model to investigate the important variables that contribute to the results in our center. I am particularly grateful to Dr. Eugene Blackstone and his colleagues for helping us with that model.

What will you tell her about screening mammography?



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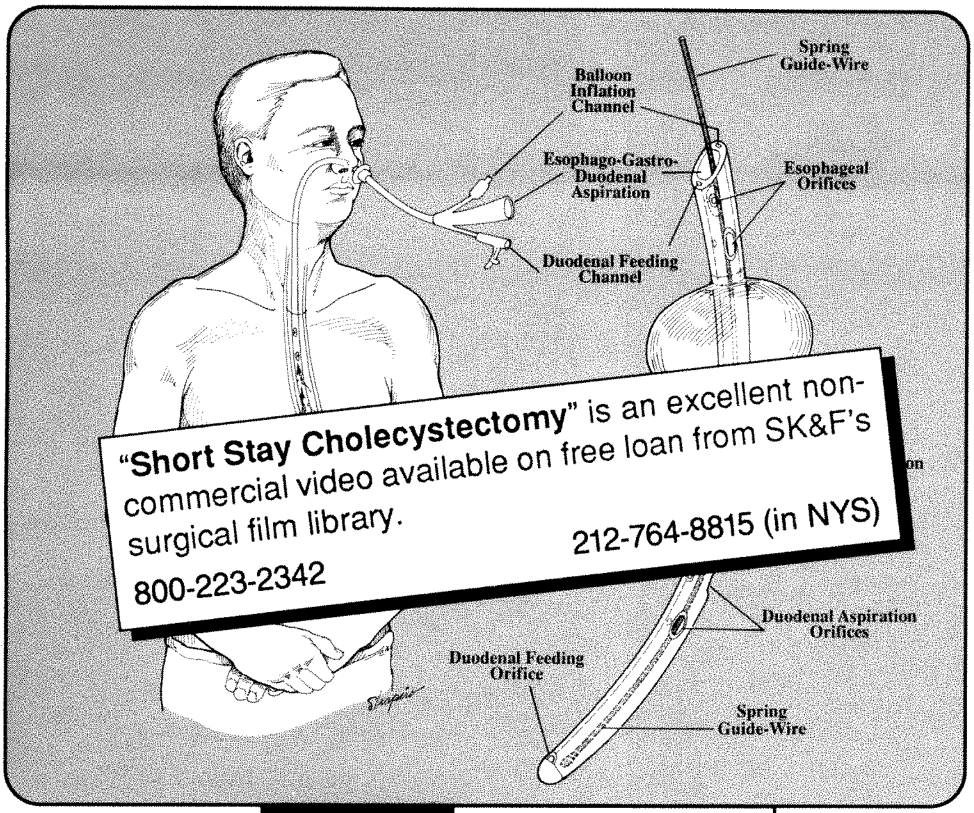

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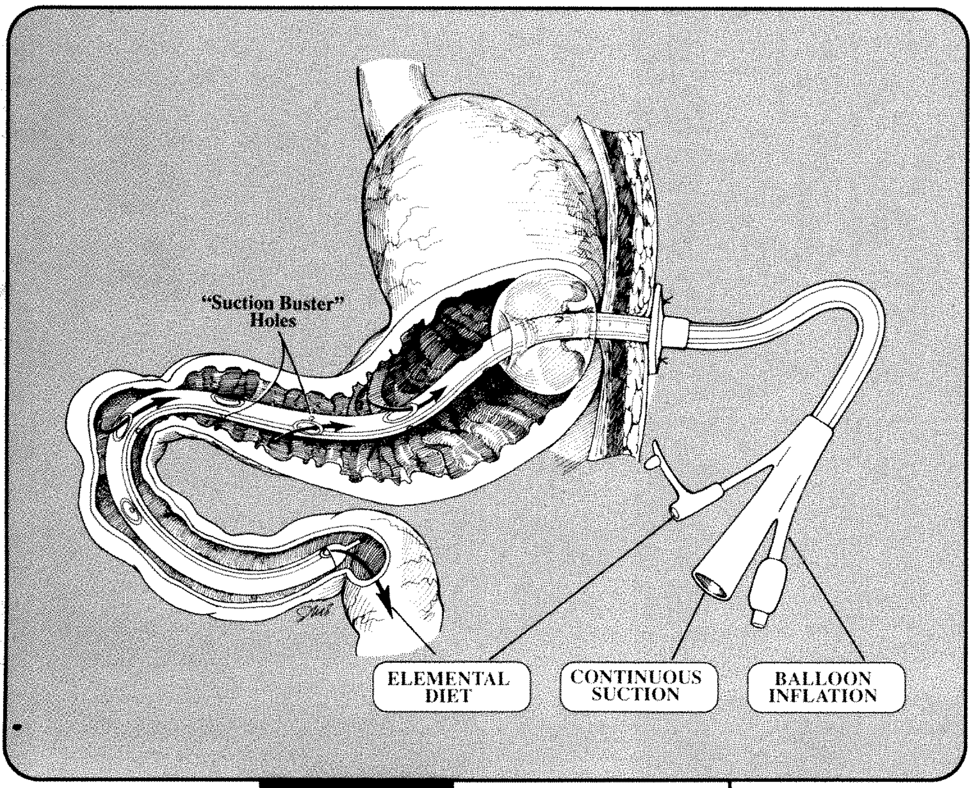

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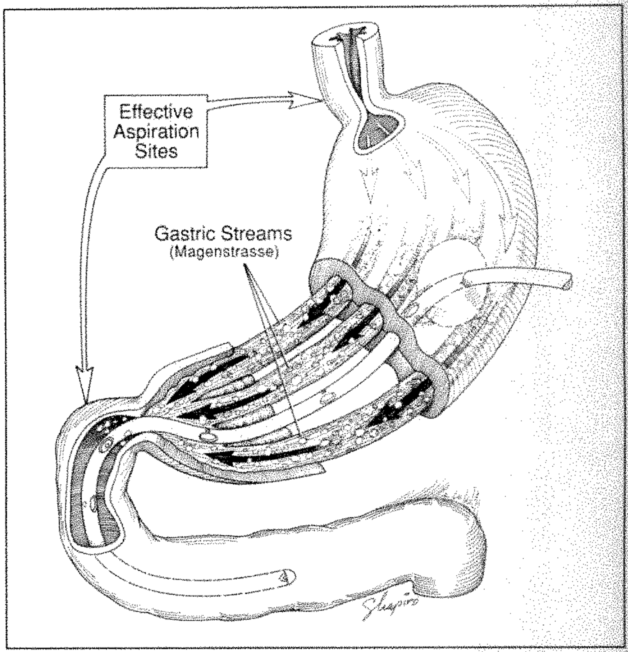
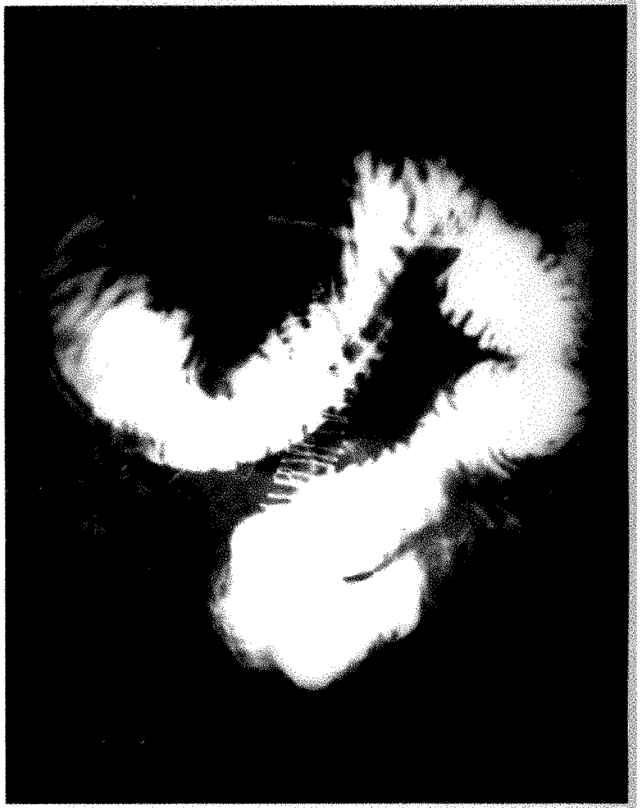
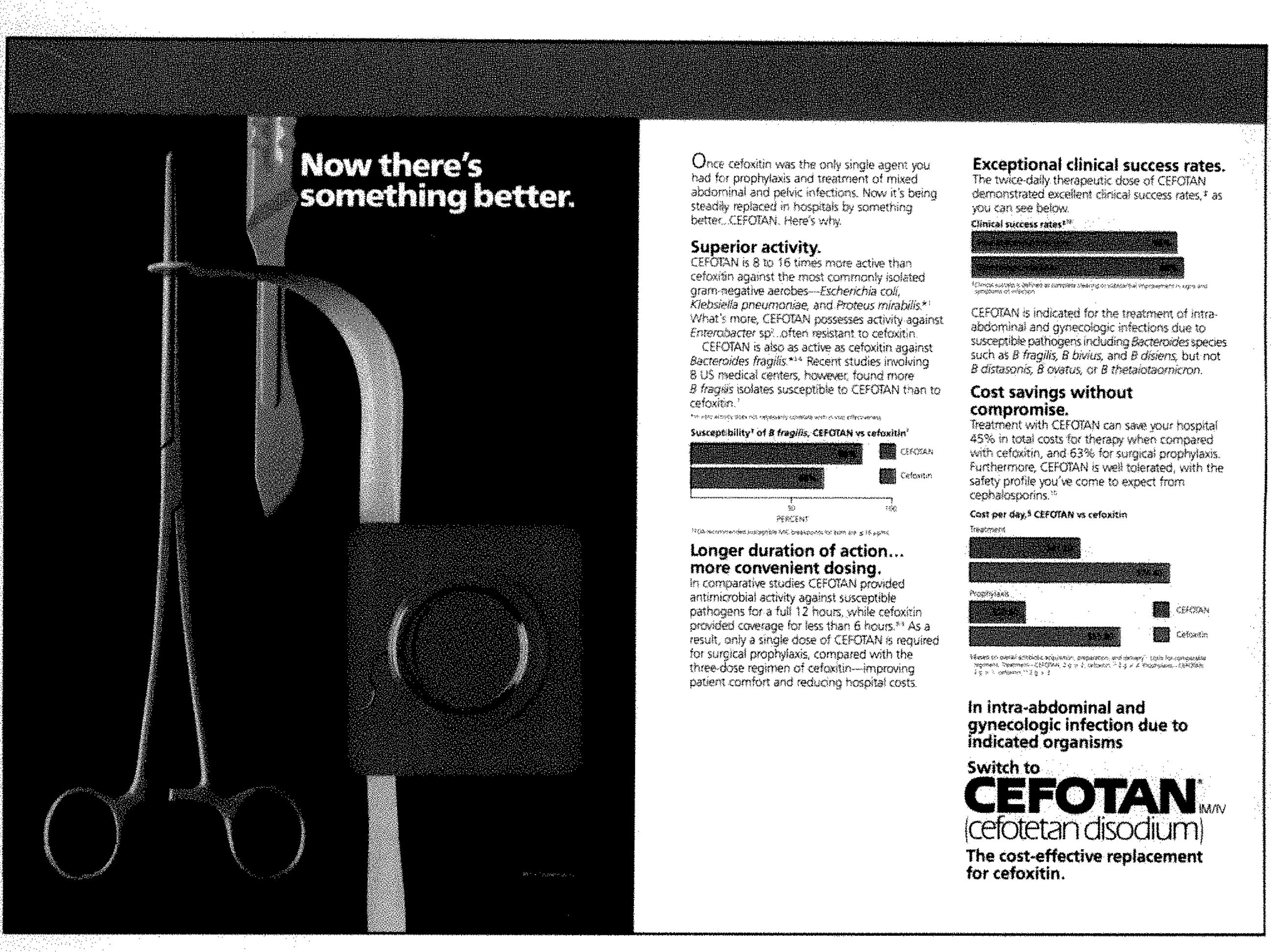


A. The functioning stomach subdivides into discrete"Magenstrasse". Any tube can only evacuate the single gastric stream within which it lies.



B. Study @ 5 minutes. Note effective removal of all excess barium flowing retrograde, none visualized to reach the stomach.

We said.[1]



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CEFOTAN is 8 to 16 times more active than cefoxitin against the most commonly isolated gram-negative aerobes—*Escherichia coli, Klebsiella pneumoniae,* and *Proteus mirabilis.**[1] What's more, CEFOTAN possesses activity against *Enterobacter* sp[2]...often resistant to cefoxitin.

CEFOTAN is also as active as cefoxitin against *Bacteroides fragilis.**[3,4] Recent studies involving 8 US medical centers, however, found more *B fragilis* isolates susceptible to CEFOTAN than to cefoxitin.[5]

Susceptibility† of *B fragilis,* CEFOTAN vs cefoxitin[5]

Longer duration of action... more convenient dosing.
In comparative studies CEFOTAN provided antimicrobial activity against susceptible pathogens for a full 12 hours, while cefoxitin provided coverage for less than 6 hours.[2,3] As a result, only a single dose of CEFOTAN is required for surgical prophylaxis, compared with the three-dose regimen of cefoxitin—improving patient comfort and reducing hospital costs.

Exceptional clinical success rates.
The twice-daily therapeutic dose of CEFOTAN demonstrated excellent clinical success rates,‡ as you can see below.

Clinical success rates‡

CEFOTAN is indicated for the treatment of intra-abdominal and gynecologic infections due to susceptible pathogens including *Bacteroides* species such as *B fragilis, B bivius,* and *B disiens,* but not *B distasonis, B ovatus,* or *B thetaiotaomicron.*

Cost savings without compromise.
Treatment with CEFOTAN can save your hospital 45% in total costs for therapy when compared with cefoxitin, and 63% for surgical prophylaxis. Furthermore, CEFOTAN is well tolerated, with the safety profile you've come to expect from cephalosporins.

Cost per day,§ CEFOTAN vs cefoxitin

In intra-abdominal and gynecologic infection due to indicated organisms

Switch to
CEFOTAN® IM/IV
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The cost-effective replacement for cefoxitin.

1. Journal Advertisement, *N Engl J Med,* 1987.

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They said.[2-9]

for treatment in obstetrics and gynecology

"Twice-daily administration of cefotetan is a highly effective single agent for the treatment of mixed aerobic-anaerobic infections in obstetric and gynecologic patients."[2]

2. Sweet RL, Gall SA, Gibbs RS, et al: Multicenter clinical trial comparing cefotetan versus moxalactam or cefoxitin as therapy for obstetric and gynecologic infections. *Am J Surg*, submitted for publication.

"Cefotetan plus doxycycline was demonstrated to be an effective and safe regimen for the treatment of acute PID as measured by early clinical response."[3]

3. Sweet RL, Schacter J, Landers DV, et al: Treatment of hospitalized patients with acute pelvic inflammatory disease: Comparison of cefotetan plus doxycycline and cefoxitin plus doxycycline. *Am J Obstet Gynecol*, submitted for publication.

for treatment in intra-abdominal infection

"98% (93/95) of cefotetan patients and 95% (41/43) of cefoxitin patients had complete resolution or improvement of their signs and symptoms of intraabdominal infection."[4]

4. Wilson SE for the Multicenter Study Group: Cephalosporin therapy in intraabdominal infections: A multicenter randomized comparative study of cefotetan, moxalactam and cefoxitin. *Am J Surg*, submitted for publication.

for prophylaxis in obstetric and gynecologic surgery

"In this evaluation, cefotetan administered in a single dose of 1 gm was more effective as a prophylactic agent than multiple, 2-gm doses of cefoxitin in reducing infectious morbidity in...cesarean section patients."[5]

5. McGregor JA, Gordon SF, Krotec J, et al: Results of a randomized, multicenter, comparative trial of a single dose of cefotetan versus multiple doses of cefoxitin as prophylaxis in cesarean section. *Am J Obstet Gynecol*, submitted for publication.

"Uterine tissue concentration was...well above the minimum inhibitory concentrations required for most gram-positive anaerobes as well as Bacteroides fragilis."[6]

6. Berkeley AS, Freedman KS, Ledger WJ, et al: Comparison of cefotetan and cefoxitin for abdominal and vaginal hysterectomy. *Am J Obstet Gynecol*, submitted for publication.

for prophylaxis in general surgery

"Cefotetan administered as a single 2-gm preoperative dose was as safe and effective as multiple doses of cefoxitin."[7]

7. Jagelman DG, Fabian TC, Nichols RL, et al: Single-dose cefotetan vs. multiple-dose cefoxitin as prophylaxis in colorectal surgery. *Am J Surg*, submitted for publication.

as a cost-effective replacement for cefoxitin

*"Cefotetan therapy cost less than cefoxitin therapy for all types of infections."**[8]

8. Sochalski A, Sullman S, Andriole VT: Cost effectiveness study of cefotetan versus cefoxitin and cefotetan versus combination antibiotic regimens. *Am J Surg*, submitted for publication.

"Cefotetan can provide significant cost savings with neither a compromise in therapeutic effectiveness nor an increased risk of toxicity."[9]

9. Hemsell DL, Wendel GD, Gall SA, et al: Multicenter comparison of cefotetan and cefoxitin in the treatment of obstetric and gynecologic infections. *Am J Obstet Gynecol*, submitted for publication.

*CEFOTAN is indicated for the treatment of intra-abdominal and gynecologic infections due to susceptible pathogens including *Bacteroides* species such as *B fragilis*, *B bivius*, and *B disiens*, but not *B distasonis*, *B ovatus*, or *B thetaiotaomicron*.

We all agree.

CEFOTAN® IM/IV (cefotetan disodium).

Does so much for so much less than cefoxitin

Please see next page for brief summary of prescribing information.

In intra-abdominal and gynecologic infection due to indicated organisms

CEFOTAN® IM/IV (cefotetan disodium)

Does so much for so much less than cefoxitin

For Intravenous or Intramuscular Use
BRIEF SUMMARY

INDICATIONS AND USAGE

TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary tract infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris*, *Providencia rettgeri*, and *Morganella morganii*).

Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.

Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.

Gynecologic infections caused by *Staphylococcus aureus*† (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus* species (excluding enterococci), *E coli*, *Proteus mirabilis*, *Neisseria gonorrhoeae*, *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*), *Fusobacterium* species,† and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species†).

Intra-abdominal infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*†), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*).

Bone and joint infections caused by *Staphylococcus aureus*.†

***NOTE:** Some strains of *Staphylococcus epidermidis* are resistant to cefotetan.

† Efficacy for this organism in this organ system was studied in fewer than ten infections.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.

PRECAUTIONS

GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state. Prothrombin times should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels of Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

CEFOTAN® (cefotetan disodium)

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approx 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approx 2-4 times the usual human dose), only 1 of 10 treated animals was affected, and the degree of degeneration was mild. Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In clinical studies the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5 percent of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4 percent of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2 percent of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2 percent of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than one percent of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

DOSAGE AND ADMINISTRATION

TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dose*	Every 12 hours
10-30	Usual Recommended Dose*	Every 24 hours
<10	Usual Recommended Dose*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED

CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21)

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Endotoxemia and Bacteremia During Hemorrhagic Shock

The Link Between Trauma and Sepsis?

BENJAMIN F. RUSH, JR., M.D., ALAN J. SORI, M.D., THOMAS F. MURPHY, M.S., SHARON SMITH, PH.D.,
JOHN J. FLANAGAN, JR., M.D., and GEORGE W. MACHIEDO, M.D.

Previous investigations of a treated model of hemorrhagic shock in the rat indicated the frequent occurrence of bacteremia that appeared to derive from the gut. This paper determines the incidence of bacteremia and endotoxemia during the acute shock period and compares this with similar observations in humans in varying degrees of shock. Studies in 26 rats indicated that bacteremia and endotoxemia was present in 50% and 87%, respectively, by the end of 2 hours at a mean arterial pressure of 30 mmHg. Observations in 50 patients admitted to the trauma unit showed that positive bacterial blood cultures were present in 56% when the admission systolic blood pressure was 80 mmHg or less ($p < 0.01$ compared with either of the other groups). Endotoxemia was noticed in two such patients. Direct access of bacteria and endotoxin to the blood stream may occur during hemorrhagic or traumatic shock and is the probable cause of subsequent sepsis in traumatized patients when no other source is apparent.

From the Department of Surgery, UMD–New Jersey Medical School and the Laboratory Service–V.A. Medical Center, East Orange, New Jersey

OVER THE PAST DECADE and a half, our laboratory, such as many others, has been engaged in the search to identify the specific injury or injuries that cause death after hemorrhagic shock. In the course of this work we became convinced that information derived from conventional shock models of the period was flawed compared with clinical experience because the models represented untreated shock, whereas all clinical experience dealt with treated shock. We developed a model in the rat in which additional Ringer's lactate solution was administered after shock to bring the blood pressure back towards normal levels. The animals also received continuous post-shock maintenance of electrolyte, fluid, and caloric balance. This model tolerates remarkable periods of shock at 30 mmHg mean arterial pressure (MAP) until decompensation has required 80% of the original bled out volume be returned to maintain the selected pressure of 30 mmHg MAP. After this vigorous regimen, almost all animals can be initially resuscitated by return of the remaining blood and the fluid therapy noted above. Nevertheless, a relentless mortality then ensues with all or almost all animals dying by the end of the third post-shock day. Although some organ damage occurs in the model, we were unable to find evidence for initial lethal injuries to any organs, and cellular damage seemed to reverse toward normal in the first 24 hours.[1]

Further experiments with this model showed that a bacteremia developed in many animals during or after shock and that by the third day after shock, almost all of the rats had bacteremia.[2] In addition, survival in this model past the third day could be achieved by treating the animals with antibiotics.[3] Most of the bacteria found in the blood of rats after shock were enteric organisms, suggesting that they came from the rats' gastrointestinal tract. By feeding rats 14C of labeled *Escherichia coli*, we were able to show that the radiolabeled *E. coli* did escape from the gastrointestinal tract during shock and appeared in the blood stream.[4]

All of the work cited above has been presented elsewhere and has been well received, but the most frequent question has been, "how does all of this correlate with what happens in the shocked human?" The following studies were designed to determine what happens to bacterial and endotoxin levels in our animal model during the acute shock period and to compare this with similar observations made in shocked patients presenting to the trauma unit at University Hospital of the University of Medicine and Dentistry of New Jersey.

Materials and Methods

Animals

Male Sprague-Dawley rats with an average weight of 350–450 g were used in all experiments. A total of 26 rats were subjected to a hemorrhagic shock model pre-

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TABLE 1. *Blood Culture and Endotoxin Results in Shocked Rats**

Time (min)	N	≥0.1 Endo Units	Gram-positive Organisms	Gram-negative Organisms
0	6	0/6	0/6	0/6
30	6	2/6 (33.3%)	2/6	0/6
60	6	4/6 (66.7%)	1/4	1/4
120	8	7/8 (87.5%)	1/4	1/4

Endotoxin levels greater than or equal to 0.1 EU in the blood of sham shocked or shocked rats at different time periods. Blood cultures were also obtained in some of the rats.

viously described.[1] To ensure a sterile and endotoxin free "shock environment," cannula tubing was flushed with pyrogen-free water before gas sterilization and sterile nonpyrogenic syringes and stopcocks were used.

Blood was collected for blood cultures and endotoxin assay *via* sterile cardiac puncture at 0 time (6 animals), 30 minutes (6 animals), 60 minutes (6 animals), and 120 minutes (8 animals). Blood for endotoxin assay was placed in heparinized (20–30 U of beef lung heparin/ml) nonpyrogenic syringes, which were placed immediately on ice.

Blood cultures were processed by the hospital laboratories at the East Orange Veterans Administration Medical Center by routine laboratory methods. Endotoxin assays were performed using the Quantitative Chromogenic Limulus Amebocyte Lysate assay (QCL-1000 by Whittaker, M.A. Bioproducts; Cat. #50-645U).

Patients

Blood specimens were collected within 3 hours of admission for culture from patients admitted to the Trauma Service. The specimens were obtained simultaneously with other blood drawn by a separate aseptic venous or arterial puncture site. Patients with perforation of any hollow viscus were excluded. Blood cultures were processed by the microbiology laboratories of University Hospital. The patients were divided into three groups: (1) those with an initial blood pressure <80 mmHg; (2) initial blood pressure >80–<110 mmHg; and (3) a control group with blood pressure >110 mmHg and injury not requiring admission to the intensive care unit (ICU) or admitted to ICU only to rule out cardiac contusion but without multisystem injury.

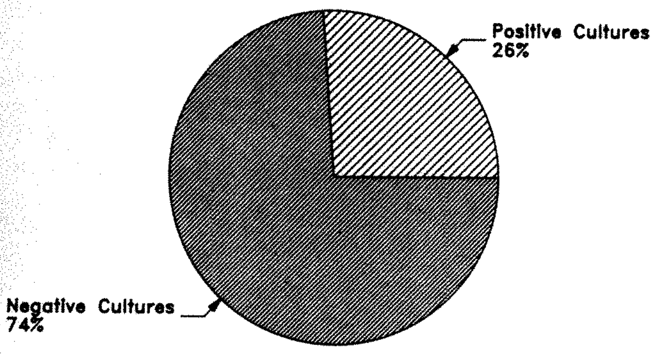

FIG. 1. Incidence of positive cultures in all patients sampled regardless of blood pressure.

Endotoxin Determinations

All glassware was depyrogenated by dry heat incubation at 200 C for a minimum of 24 hours. All nonheat-resistant materials were rendered pyrogen-free by rinsing with pyrogen-free water and subsequently sterilizing with ethylene oxide. Water used for reconstitution and as a diluent was sterile and nonpyrogenic. Blood was aseptically drawn and immediately placed on ice. The blood was centrifuged at 3000 g for 10 minutes at 4 C. Plasma was diluted 1:10 in pyrogen-free water and heated for 10 minutes at 75 C. Quantitative chromogenic assay kits were used for endotoxin determinations. Fifty microliters of the test sample was incubated with an equal volume of Limulus lysate for 30 minutes at 37 C. One hundred microliters of substrate was added and incubated for 3 minutes at 37 C. The reaction was then stopped with 200 μl of 50% acetic acid. Absorbance was read at 405 nm with a Beckman DU-6 spectrophotometer (Beckman Instruments, Inc., Irvine, CA). Standard absorbance curves using *E. coli* 0111: B4 endotoxin prepared by the phenol-water method were performed daily. Each standard and sample specimen was determined in duplicate and corrected for its own blank. Blanks were obtained by adding acetic acid before the substrate. The test detected 0.01 ng of standard endotoxin/ml plasma equal to 0.1 endotoxin units (EU)/ml. Plasma with that value or greater were considered positive.

Statistical Analysis

Statistical significance between groups was determined using the chi-square test.

Results

None of the six sham-shocked rats had significant blood levels of endotoxin or positive bacterial cultures. On the other hand, endotoxin levels of 0.1 EU or higher were observed in 33% of six animals after only 30 minutes of shock and in 88% of the animals after 2 hours of shock. Positive bacterial cultures for gram-positive or gram-negative bacteria or both were found in 50% of rats sampled at 1 and 2 hours of shock (Table 1).

Blood cultures were obtained from 50 patients admitted to our trauma unit; of these 26% were positive (Fig. 1). Twenty-five of these patients were admitted with systolic blood pressures of 110 mmHg or higher and only

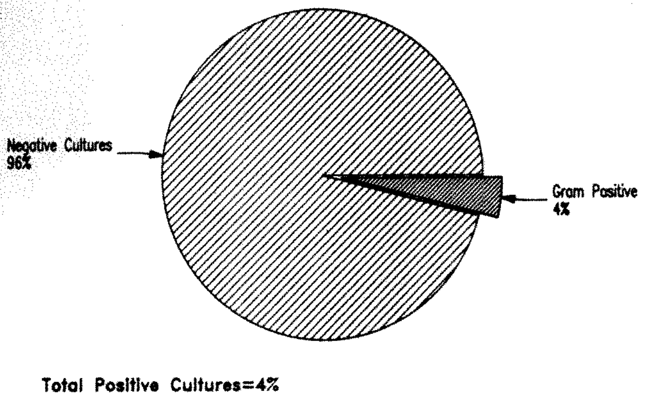

FIG. 2. Incidence of positive blood cultures in patients admitted to the trauma center with blood pressures greater than or equal to 110 mmHg.

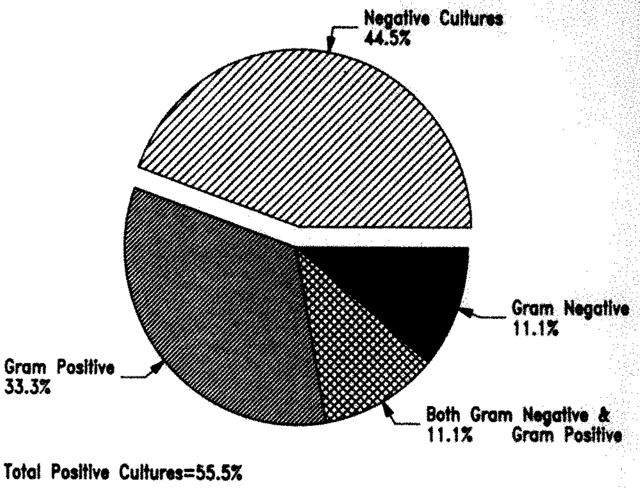

FIG. 4. Incidence of positive blood cultures in patients admitted to the trauma center with blood pressures of 80 mmHg or less.

one patient had a positive blood culture (Fig. 2). This was a gram-positive organism but was not a contaminant as indicated by the fact that the blood cultures were positive for the same organism on two additional days. Despite their higher blood pressures, many of these patients had serious injuries. Three patients (12%) eventually died. The patient with a positive blood culture survived.

Seven patients had systolic blood pressures of greater than 80 mmHg but less than 110 mmHg; of these, two patients had positive blood cultures and both patients survived (Fig. 3). One patient in this group (14%) eventually died.

Eighteen patients were admitted with systolic blood pressures of 80 mmHg or less. In this group there were 10 patients with positive blood cultures (56%). This was a seriously injured group. Average admission blood pressure for the group was 45 mmHg, and all but two patients eventually died. Four deaths occurred in the emergency room, four in the operating room, five in the first 24 hours, two in the first week, and one in the second week. Of the 10 positive blood cultures, six contained gram-positive organisms, two gram-negative organisms, and two contained both (Fig. 4). This was the only group of patients who had blood cultures positive for gram-negative organisms. Figure 5 illustrates the relationship between blood pressure on admission and the presence of positive cultures.

The difference between the lowest blood pressure group and the other two groups in terms of the number of positive cultures was highly significant ($p < 0.01$). Blood samples for endotoxin levels were obtained in 10 patients. In six patients, blood pressure was over 80 mmHg on admission, and none had a clinically significant level of endotoxin in their blood although some were "high normal." Of the four patients with blood

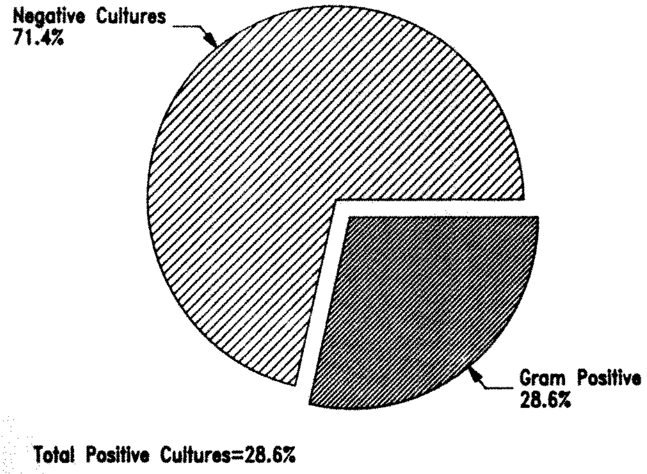

FIG. 3. Incidence of positive blood cultures on patients admitted to the trauma center with blood pressure greater than 80 mmHg but less than 110 mmHg.

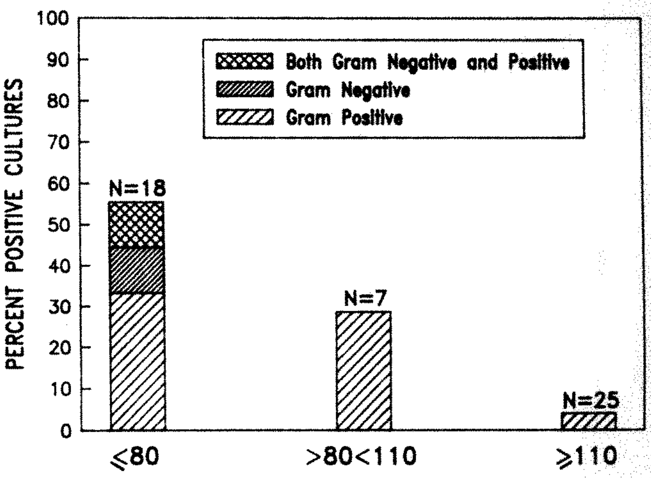

FIG. 5. Correlation of blood pressure with the incidence of positive blood cultures.

pressures of 80 mmHg or less, two had significant endotoxin levels.

Discussion

For centuries physicians have looked at the gut with great suspicion as the source for a multitude of illnesses. Purging was one of the few options available in the therapy of our medical forebears and was often used.[5] In more modern times, several lines of evidence have focused attention on the role of the gut in patients after hemorrhagic shock. Fine[6] produced a series of papers suggesting that the absorption of endotoxin from the gut in the patient in hemorrhagic shock combined with a crippling of the reticuloendothelial system in the liver led to irreversibility of the shock state. An insightful group of papers from Louisville[7,8] have suggested that the organ failure seen after trauma and shock are primarily related to ensuing infection. Deitch and coworkers have demonstrated in a number of elegant experiments in rats and mice that burns and trauma among other conditions lead to the translocation of bacteria from the gut to the mesenteric lymph nodes and sometimes other abdominal organs.[9]

From both our experimental and clinical data, we suggest that one of the important initiating events in the syndrome that follows hemorrhagic shock is the direct absorption of bacteria and endotoxin into the blood of the traumatized, hypotensive patient. We know that cell membranes become hyperpermeable in severe hemorrhagic shock.[10] It should not be surprising that sheets of tissue made up of such shocked cells also become hyperpermeable not only in the gut mucosa but also in capillaries and perhaps lining membranes elsewhere. The frequent finding of gram-positive as well as gram-negative organisms in our traumatized patients may be due to direct injury to the skin or to hyperpermeability of skin structures or of membranes of the upper aerodigestive tract.

We assume that this early bacteremia combined with the well-known damage that occurs to the immune system in the shocked, traumatized patient[11,12] sets the stage for the sepsis and multiorgan failure so often seen in our intensive care units. Like the burned patient and the patient with severe acute pancreatitis, the patient with severe trauma and hemorrhagic shock is subjected to a two-phase process. The first phase is a massive fluid shift and initial extracellular fluid depletion. This may be accompanied by membrane hyperpermeability with bacteremia, which leads to the second phase, which is the septic state. Clinicians have learned to treat the first phase effectively with appropriate replacement of blood and electrolyte fluid. We are still struggling, however, to solve the riddle of appropriate treatment or prevention of the second phase.[13] It is the second phase with its accompanying multiple organ failure that now constitutes what we used to call irreversible shock.[14]

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DISCUSSION

DR. EDWIN A. DEITCH (Shreveport, Louisiana): I would like to start off by congratulating and thanking Dr. Rush for not only a nice presentation but for the privilege of reviewing his manuscript.

Dr. Rush has been looking at this field for a number of years, and the data he showed you is very impressive. We, too, have been interested in failure of the gut mucosal barrier, and over the last five years we have used a number of different experimental models to determine under what conditions the gut barrier to bacteria is lost.

We have coined the term "bacterial translocation" to describe this phenomenon, and last year at this meeting, we presented data showing that protein malnutrition and endotoxemia led to failure of the gut mucosal barrier, sepsis, and death in rodents.

We also have been interested in the hemorrhagic shock model. I would like to show you some histology that characterizes the mechanism by which the barrier is lost.

(Slide) Our shock model is not as severe as the one used by Dr. Rush. In our model, rats are subjected to 30 minutes of shock (30 mmHg). In the shocked animal, one can see that there is subepithelial blebbing and edema formation as the intestine is injured.

This slide shows a section of intestine where the mucosal barrier is lost and bacteria are invading the lamina propria.

In attempting to determine the mechanisms responsible for gut failure, we have found that when bacteria translocation occurs, generally one or more of three primary mechanisms are occurring. First is bacterial overgrowth in the intestines, resulting from disruption of the ecology of the gut microflora. This phenomenon is not the explanation for why bacterial translocation occurs after shock.

Secondly, host immune defenses are important in maintenance of physiologic bacterial barrier.

From our studies, it appears that ischemia with physical disruption of the mucosal barrier is the mechanism by which bacterial translocation occurs.

Our concept is that the first line of defense of the gut is either portal blood or lymphatics. If bacteria escape in the portal blood, then liver culture will be positive. If they escape through the lymphatics, then the mesenteric lymph nodes become positive. Positive blood cultures, I think, are only a late sign of gut failure, and I would like to ask Dr. Rush to address the question of whether he thinks a positive blood culture is a *sine qua non* of gut failure.

We found in our shock model that if we pretreated the animal with allopurinol, which blocks xanthine oxidase activation and subsequently oxidant generation, shock-induced bacterial translocation is reduced.

Similarly, if we feed the animals a tungsten diet to inactivate xanthine oxidase, we prevent translocation, and if we scavenge hydroxyl radicals with DMSO, we can prevent translocation.

So we believe that shock-induced bacterial translocation is a reperfusion injury. Additionally, treatment with allopurinol, as well as the tungsten diet also prevents the shock-induced mucosal injuries.

I would like to ask the authors three questions. First, where did the bacteria come from? With gram positive bacteria it is likely that skin, as well as the gut, may be the source.

Have you any information on whether these bacteria are Enterococcus or Staphylococcus, since both Staphylococcus and Enterococcus can originate from the gut. Could bacteria have originated from I-V lines placed in the emergency room?

Secondly, is a positive blood culture too insensitive a test? That is, one needs to have a preterminal patient in which everything has failed, including the liver, the RES system, and so on, before the blood cultures become positive.

And the last question is: What do you speculate the mechanism is by which this is occurring, and do you have any evidence or any plans for further studies to try to reverse this gut failure?

DR. RAYMOND FLETCHER (Nashville, Tennessee): I, too, rise to compliment Dr. Rush on the studies he has done over the years in this particular area, and I have one general comment and a couple of questions.

Dr. Rush, you are aware that the rat mesenteric circulation is very sensitive to vasoactive substances, and I wonder if you have done this in other models, or whether there is a better model to make it more like the human model.

Secondly, in your patients you presented data that demonstrated that there was a very high positive blood culture rate in patients with blood pressures less than 80 mmHg.

Is there a relationship between the time that these patients were in shock and the degree of positivity of their blood cultures, and what percentage of your patients that have survived with positive blood cultures went on to develop systemic sepsis?

DR. FRANK G. MOODY (Houston, Texas): As Dr. Rush has pointed out, his patients had very severe hemorrhagic shock. Most of them died. In addition, his experimental model was also a severe shock model.

At the University of Texas, Houston, and the Hermann Hospital, we have been interested in the other group, the multiple organ failure group, and, to put it in perspective, we see about 2000 injured patients a year. About 1200 make it to the surgical intensive care unit for various periods of time, and about 50 get multiple organ failure.

What is interesting about this group is that most of them had an episode of hemorrhagic shock from which they had been successfully resuscitated, and they have also had their wounds repaired.

By about the seventh day, they begin to appear septic, although in about only half of them are we able to get positive blood cultures at that point in time.

We have taken this to the laboratory in several different ways, and I only mention two. One is to "wire" opossums in order to study their myoelectric potentials and to look at what the gut is doing in terms of propulsion. And it is interesting that just with moderate shock (and by that I mean 60 millimeters of mercury for 60 minutes in an opossum, from which they all recover), it has a profound effect on slowing the peak activity of the myoelectric potentials, and this is what is associated with propulsion down the gut.

So I wouldn't dismiss the concept that bacterial overgrowth may possibly play a role.

Dr. Deitch would be very quick to point out to you that he has not studied small bowel enteric flora, and yet he shows us pictures of the small bowel as being the route of entry of the bacteria.

A second part of the study carried out by Dr. Miller at our institution has involved looking at the small bowel epithelium in translocation. He and his colleagues have found that even moderate shock is associated with epithelial changes at 7 days in rats sustained by parenteral alimentation. There is also a translocation to the lymph nodes and occasionally into the spleen of enteric organisms, but it is not very profound.

I, therefore, would ask Dr. Rush if he has been curious enough to study some survivors, to tell us what their endotoxin levels were and whether, in fact, he has been able to get positive blood cultures similar to what he has obtained in the patients in the emergency center.

DR. R. NEAL GARRISON (Louisville, Kentucky): I wish to congratulate Dr. Rush and his co-authors on a simple but elegant study of endotoxemia and bacteremia during and following hemorrhagic shock both in the clinical and laboratory setting.

This paper clearly links the experimental findings of these authors and the work of Dr. Deitch with the clinical observations of the occurrence of infection and organ system failure that we in Louisville have been studying for several years.

I have two questions for the authors. First, from where were the clinical blood cultures drawn—the venous or the arterial side of the circulation? If the bacteremia is truly of gut origin, then one would expect a higher percentage of positive arterial cultures compared to venous blood samples that have passed through not only the hepatic portal reticuloendothelial system filter, but also the systemic circulatory system of wandering macrophages.

Secondly, along similar lines that Dr. Deitch has previously asked, would the authors care to speculate on the mechanism and timing of the bacteremias? We, as well as others, have shown that under severe stress gastrointestinal flow is greatly diminished. Does the bacteremia occur during this low flow state or with subsequent reperfusion? This latter question would have implications for preventative therapy, such as oxygen-free radical therapy during resuscitation.

DR. HARVEY J. SUGERMAN (Richmond, Virginia): I would just like to give some confirmatory data with regard to Dr. Rush's hypothesis that what is probably going on is major permeability injury. Using a computerized gamma camera to evaluate increased pulmonary permeability, we have found that critically ill, septic ICU patients with a positive study had double the ventilatory time and triple the ICU and hospital stay than patients without a permeability injury. Do you have evidence for increased permeability in other organs, such as in the lung, in these patients?

DR. WATTS R. WEBB (New Orleans, Louisiana): Dr. Rush's study gives us an understanding of some observations we made nearly 25 years ago. We had observed the gross and microscopic changes that occurred in the small and large bowel with hemorrhagic shock. We subjected a group of dogs to total exenteration of the small and large bowel and found that these animals tolerated hemorrhagic hypotension much better than the relatively normal animals. I think now we have some further explanation for this.

DR. BENJAMIN F. RUSH (Closing discussion): I will certainly do my very best to keep all of these questions straight.

Dr. Deitch was curious as to what our information was—as to whether in our human patients blood cultures only were positive or whether other tissues were cultured. To date, all we have available are blood cultures. Of the results from patients, the cultures were entirely from the venous side, either from catheters or from special sites that our research Fellows selected and prepared appropriately.

We were reassured by the fact that our unshocked patients showed negative cultures uniformly, and we assumed that that meant that the incidence of contamination was low or nonexistent, which I guess is a response to the question that I think that Dr. Deitch also asked: How about contamination from I-V lines or other sites?

All patients in this study, whether shocked or unshocked, were injured patients and, there were three deaths in the group of patients who came with blood pressures above 110. There was one death in the group of seven patients who came in with blood pressures between 80 and 110. In most instances, these patients had only single organ injuries or other events. For instance, in the unshocked patients, there was one patient who subsequently died of a pulmonary embolus and one who died of a brain injury.

As for the question as to further studies: I think there is no question that we are going to continue to look at where these bacteria come from and what are the most important sites to be considered, either in terms of prophylaxis or appropriate intervention.

Dr. Moody brought up the question of the great severity of the shock in our patients. There is no question that the group that was admitted with blood pressures of 80 or below was very severely shocked. As I may have mentioned, the mean pressure for the entire group was 45 millimeters of mercury, and it doesn't take much imagination to show that in order to get that rather low mean, some of those patients arrived with a blood pressure of zero and others were fairly low.

Nonetheless, you will notice that there were also some with positive cultures in the group who arrived with pressures above 80, between 80 and 110; so while severity seems to be correlated with the frequency of positive cultures, it is possible to have positive cultures at somewhat higher levels of blood pressure in injured patients.

I might add one other feature. That is, you will notice that while our shocked model is very severe, the data I presented here was for positive blood cultures obtained at measures of 30 mm of mercury for the first 30, 60, and 120 minutes of shock. Obviously, we are already beginning to find positive cultures after as little as 30 minutes of shock in that group.

Finally, have we studied survivors in our patients. In the most severely shocked patients we had only two survivors, so we haven't much to follow with them. We are currently attempting to get sequential studies in those patients with negative and positive blood cultures to determine if, in fact, clinically important sepsis shows up at a later date and how that can be correlated with what we find in the blood of patients on admission.

Dr. Garrison asked about the blood cultures and the source, and I think I have responded to that.

What about the mechanism and the timing of the bacteremia? I believe that will be shown only through future studies. We can speculate, as we already have in this paper, on where the contamination comes from and have suggested membrane hyperpermeability. We suspect that the bacteria don't come from the gut alone, but since we live in a world where bacteria resides in our skin and most of our other organs that connect with the outside world, depending a little bit on the type and dimension of the injury and the depression of the immune system, we speculate that you may well derive bacteria from any such site, that is, skin, lungs, oral cavity, and upper airways, as well as the gut.

Dr. Fletcher wanted to know about the time it took to deliver these patients and how that correlated with bacteremia. Unfortunately, we haven't done that correlation. I think that is an interesting one. We do have the data and we will be going back to look at that.

The time to sepsis after injury in our patients? Again we have that data, but are still accumulating enough follow-ups for significant observations.

Finally, Dr. Sugerman wants to know about the evidence of increased permeability in other organs. We haven't studied that yet, Dr. Sugerman. We suspect that it happens at a number of sites. In our rat data, it is interesting to note there is a two-phase process following resuscitation. The number of rats with bacteremia decreases transiently and then increases again subsequently, so there seems to be a sort of double phase as you resuscitate the animal; some go on to recovery and some go on to get worse. The initial bacteremia is almost entirely gram-positive while the late bacteremia is gram-negative or mixed.

And finally, Dr. Watts Webb, I did notice your paper. I think the explanation for your result is as you suggest.

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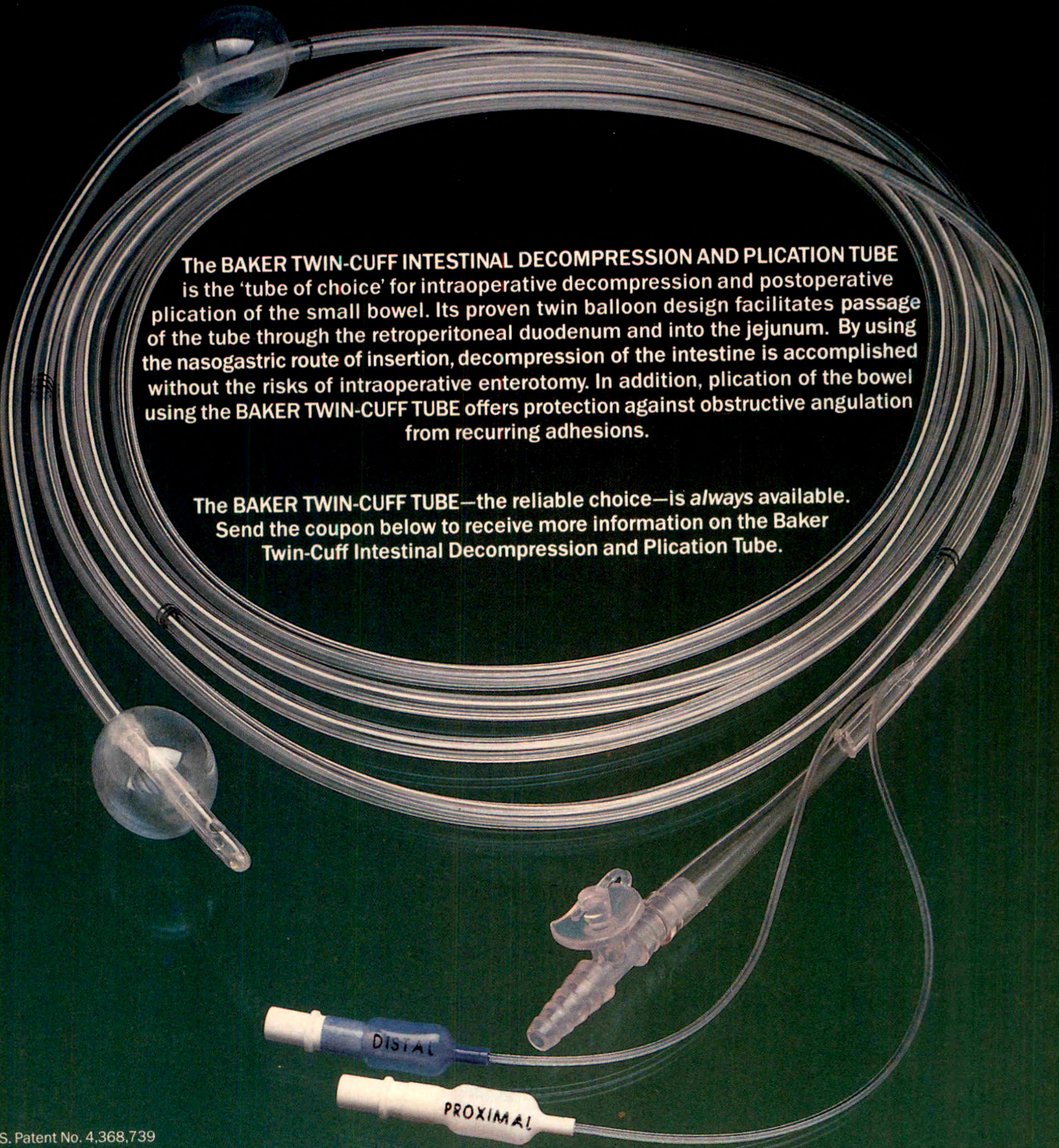

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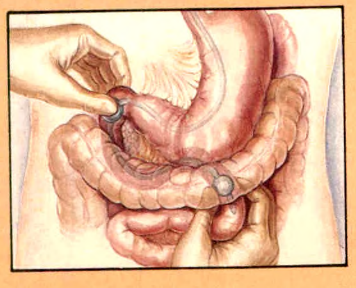

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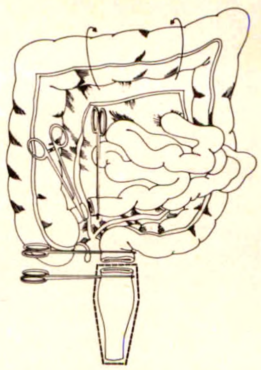

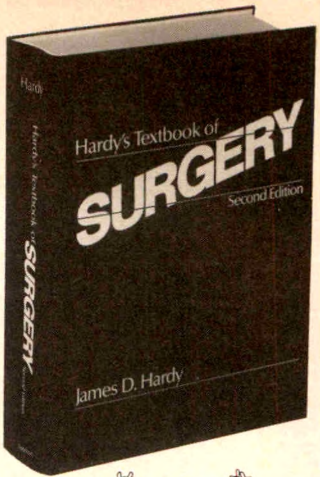

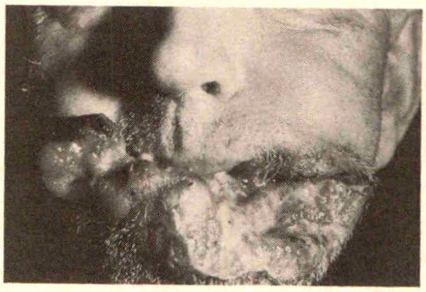

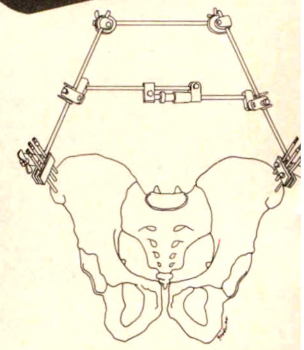

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The Atriocaval Shunt

Facts and Fiction

JON M. BURCH, M.D., DAVID V. FELICIANO, M.D., and KENNETH L. MATTOX, M.D.

During the past 11 years, 31 patients with major juxtahepatic venous injuries were treated with the atriocaval shunt. Penetrating injuries occurred in 27 patients (87%), and injuries from blunt trauma occurred in four patients. Shock was present on admission in 28 patients (90%). Resuscitative thoracotomy for cardiovascular collapse was required in 13 patients (42%). Juxtahepatic venous injuries included the vena cava in 23 patients (74%) and the hepatic veins alone in five patients (16%). One patient had an isolated portal venous injury, and two patients died before their vascular injuries could be delineated. Technical problems related to the shunt occurred in seven patients. Most were related to delays in placement or problems encountered in obtaining vascular control of the suprarenal vena cava. Major hepatic resection was performed in 11 patients (35%). Twenty-five patients died of their injuries. No patient survived who required resuscitative thoracotomy, hepatic resection, or when technical problems with the shunt occurred. Six patients (19%) survived and were discharged from the hospital. All sustained gunshot wounds to the retrohepatic vena cava. Four of the six survivors had serious postoperative complications, but none were related to the shunt. Major juxtahepatic venous injuries are highly lethal. The atriocaval shunt will permit the salvage of some patients where other methods are not possible. Avoidance of delay and alternative shunting techniques that eliminate difficult maneuvers may improve survival in the future.

From the Cora and Webb Mading Department of Surgery,
Baylor College of Medicine, and The Ben Taub
General Hospital, Houston, Texas

THERE ARE FEW TECHNICAL MANEUVERS in surgery as dramatic or desperate as the use of the atriocaval shunt in the management of patients with injuries to the major juxtahepatic veins. Invariably, the patient is on the brink of exsanguination and the surgeon is unlikely to attain hemostasis using conventional techniques. These injuries are fortunately rare, but when they are encountered, the surgeon must have a plan for controlling the hemorrhage and repairing the vascular injuries. The usual approach has been with the use of the atriocaval shunt.[1-5] Some surgeons, however, have expressed concern about difficulties or high mortality rates associated with the use of the shunt.[6-9] The atriocaval shunt has been used at this institution to treat many injuries involving the suprahepatic vena cava, retrohepatic vena cava, and hepatic veins which have been encountered. The purpose of this review is to analyze the procedures performed during the past 11 years emphasizing the indications, results, techniques, and pitfalls with the atriocaval shunt in the management of these lethal injuries.

Clinical Material and Methods

From January 1, 1977 through November 20, 1987, 31 injured patients were treated at Ben Taub General Hospital in Houston, Texas, with the atriocaval shunt. All patients in this series are listed and numbered individually for reference. Table 1 lists all nonsurvivors who required resuscitative thoracotomy, Table 2 lists all nonsurvivors who did not require resuscitative thoracotomy, and Table 3 lists all survivors.

All patients were males with an average age of 30 years (range: 14–64 years). Penetrating injuries occurred in 27 patients (87%), and included 21 with gunshot wounds and six with stab wounds. Blunt trauma was responsible for the injuries of four patients, including two motorcycle accidents, one automobile accident, and one fall.

Prehospital care was administered by the paramedics and emergency medical technicians of the Houston Fire Department. During the study period, average prehospital time was reduced from 40 minutes in 1977 to 25 minutes in 1987. On arrival to the emergency center,

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TABLE 1. *Patients Requiring Resuscitative Thoracotomy**

No.	Age (Years)	Mechanism	Time†	INJ‡	Associated Injuries§	Severe Liver Injury	Hepatic Resection	Lowest pH	Lowest Temp	Length of Operation	RBC‖ Units Given
1	41	GSW	15	SHVC	Diaphragm, lung	No	No	NA	30.5	0.75	8
2	23	GSW	30	RHVC	Diaphragm, aorta	No	No	7.09	NA	3.75	49
3	27	GSW	30	RHVC PV	—	Yes	Lobe	6.98	28.6	1.5	15
4	NA	GSW	30	¶	Kidney	Yes	Lobe	6.90	28.5	0.75	13
5	NA	BT	30	RHVC HV	Brain, hilum of lung	No	No	7.23	NA	0.75	7
6	32	GSW	30	RHVC	—	Yes	Lobe	7.12	31.5	1.75	36
7	32	GSW	15	HV	—	Yes	No	NA	NA	0.25	0
8	23	SW	15	RHVC	Stomach	No	No	NA	NA	0.5	1
9	NA	GSW	20	RHVC HV	Diaphragm, lung, colon, small bowel, spleen	Yes	Segment	6.96	31.1	1.0	12
10	NA	GSW	30	HV	Diaphragm, lung	Yes	Lobe	7.10	30.1	1.5	30
11	NA	GSW	20	HV	Diaphragm, lung	Yes	No	7.00	30.5	1.0	10
12	14	BT	10	RHVC HV	Brain	Yes	No	6.87	32.0	1.25	48
13	20	SW	60	SHVC	Diaphragm, lung	No	No	NA	37.6	0.75	10

* All had aortic clamps placed and all exsanguinated in the operating room.
† Time from admission to operating room.
‡ Juxtahepatic vascular injuries.
§ All had liver injuries.
‖ Red blood cell.
¶ Undetermined.

GSW = gunshot wound.
BT = blunt trauma.
SW = stab wound.
SHVC = Suprahepatic vena cava.
RHVC = Retrohepatic vena cava.
PV = Portal vein.
HV = Hepatic vein.

patient resuscitation and subsequent treatment was performed by surgical residents under the supervision of the senior surgical faculty.

Shock, defined as blood pressure less than 80 mmHg, was present in 28 patients (90%) on admission. Patients who had cardiopulmonary arrest within a few minutes of arrival to the emergency center, or while in the emergency center, underwent immediate left anterolateral thoracotomy with cross-clamping of the descending thoracic aorta and were taken expeditiously to the operating

TABLE 2. *Nonsurvivors not Requiring Resuscitative Thoracotomy*

No.	Age (Years)	Mechanism	Time*	INJ†	Associated Injuries‡	Severe Liver Injury	Hepatic Resection	Aortic Clamp	Lowest pH	Lowest Temp	Length of Operation	RBC§ Units Given
14	20	BT	180	RHVC HV	—	Yes	Total	Yes	NA	NA	1.75	12
15	NA	SW	NA	HV	Small bowel, colon	No	No	Yes	NA	NA	NA	NA
16	27	SW	225	RHVC	Diaphragm, lung	No	Lobe	Yes	7.06	28.5	3.0	45
17	41	SW	180	RHVC	Diaphragm	No	No	Yes	NA	NA	NA	30
18	21	BT	20	RHVC HV	—	Yes	Lobe	Yes	6.95	30.5	2.0	35
19	NA	SW	20	RHVC HV	Small bowel, lung	No	Lobe	Yes	NA	30.0	1.75	24
20	45	GSW	10	HV	Renal artery, renal vein, diaphragm, lung	Yes	Lobe	Yes	7.21	34.0	1.5	18
21	26	GSW	30	RHVC	—	No	No	Yes	7.26	32.0	1.0	35
22	59	GSW	‖	PV	Gall bladder	No	Lobe±	No	7.19	34.0	3.75	10
23	24	GSW	45	RHVC	Diaphragm, kidney, renal vein	Yes	No	No	7.20	29.5	2.5	66
24	33	GSW	10	¶	—	Yes	No	Yes	NA	NA	0.5	6
25	64	GSW	‖	SH	—	No	No	Yes	6.93	34.0	1.5	15

* Time from admission to operating room.
† Juxtahepatic vascular injuries.
‡ All had liver injuries.
§ Red blood cell.
‖ Shunt placed at second operation for rebleeding.

¶ Undetermined.
GSW = Gunshot wound.
SW = stab wound.
BT = blunt trauma.
± Lobectomy performed at third operation for hepatic necrosis.

TABLE 3. *Survivors*

No.	Age (Years)	Mech-anism	Shock	Time*	INJ†	Associated Injuries‡	Severe Liver Injury	Aortic Clamp	Lowest pH	Lowest Temp	Length of Operation	RBC§ Units Given	Length of Stay
26	30	GSW	No	540	RHVC	Diaphragm	No	Yes	7.38	35.5	4.0	9	11
27	22	GSW	No	210	RHVC HV	Diaphragm, lung	No	No	7.15	29.0	7.0	40	36
28	28	GSW	Yes	10	RHVC	Skull fracture, extremity	No	No	7.29	33.0	5.5	18	14
29	21	GSW	Yes[‖]	15	RHVC	Stomach extremity	No	No	NA	NA	NA	34	63
30	23	GSW	Yes	150	RHVC	Spinal cord, extremity, diaphragm, lung	No	Yes	7.18	32.5	4.5	35	103
31	26	GSW	No	15	RHVC HV	Esophagus, stomach, spleen, diaphragm	No	No	7.15	33.1	3.5	43	198

* Time from admission to operating room.
† Juxtahepatic vascular injuries.
‡ All had liver injuries.
§ Red blood cells.
[‖] BP 0 on admission.
GSW = gunshot wound.
NA = not available.

room.[10] Eleven patients (35%) underwent resuscitative thoracotomy in the emergency center. In addition, two patients had cardiovascular collapse in the operating room before the induction of anesthesia and required resuscitative thoracotomy. Overall, 13 of 31 patients (42%) required resuscitative thoracotomy.

The length of time from admission to the time the patient arrived in the operating room was determined for 28 patients. There were 21 patients (68%) operated on within 30 minutes of arrival in the emergency center, and eight patients operated on between 45 and 540 minutes after admission. Two patients had rebleeding after repair of injuries without the atriocaval shunt and had shunts placed to control the hemorrhage during reoperation. Both patients had missed injuries, and their times from admission to operation were not determined. For one patient, this time could not be determined with precision.

The diagnosis of injuries requiring an atriocaval shunt was made at the time of operation in all cases. Often, injuries involving the juxtahepatic vasculature were suspected on the basis of the location of missiles in and around the lower thoracic and upper lumbar spines on chest x-rays. At the time of abdominal exploration, profuse venous hemorrhage from behind the right lobe of the liver, into the lesser sac, or posterior to the porta hepatis suggested injury to the retrohepatic vena cava. Hemorrhage near the diaphragm suggested injury to either the suprahepatic vena cava, retrohepatic vena cava, or hepatic veins. Patients with severe parenchymal liver injuries, in whom a Pringle manuever failed to control hemorrhage, were suspected of having injuries to the retrohepatic vena cava or hepatic veins. Unusual presentations occurred in four patients: three had hemorrhage into the right hemithorax and one had a pericardial tamponade.

The incisions used were dependent on the patient's initial condition. Nine patients requiring resuscitative thoracotomy had bilateral anterolateral thoracotomies before midline abdominal incisions. Of the four remaining patients treated with resuscitative thoracotomy, two had left anterolateral thoractomies extended into left thoracoabdominal incisions and two had median sternotomies connected to midline laparotomies. Three patients underwent initial right anterolateral thoracotomies. When the hemorrhage was noted to come through a defect in the diaphragm, midline incisions were performed. On recognition of the nature of the injury, two patients had conversions to bilateral anterolateral thoracotomies and one had an extension into a right thoracoabdominal incision. The remaining 13

TABLE 4. *Juxtahepatic Vascular Injuries in 31 Patients*

Injury	No. of Patients
RHVC only	11
RHVC and HV	8
RHVC and PV	1
SHVC only	3
HV only	5
PV only	1
Undetermined	2
Total	31

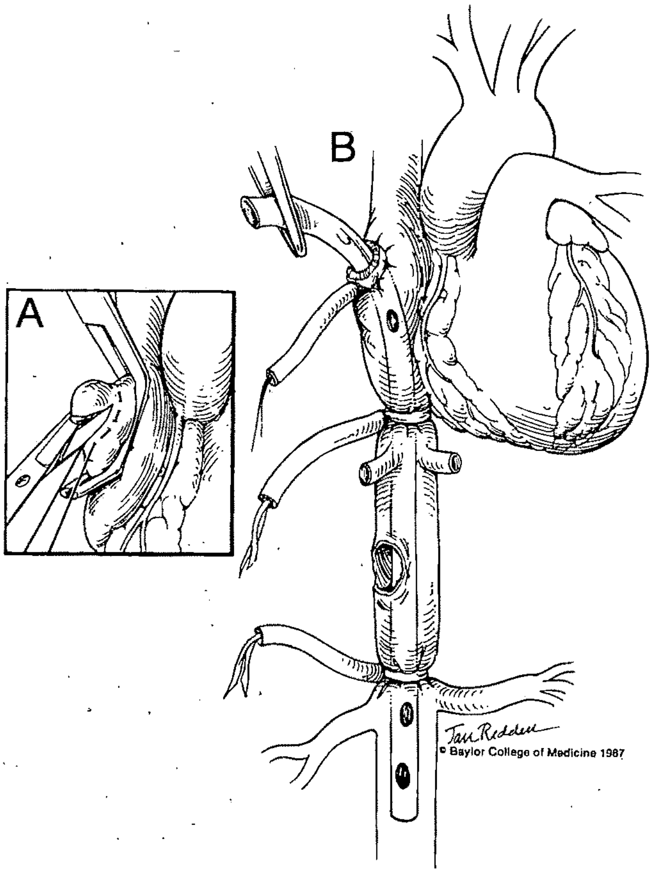
RHVC = Retrohepatic vena cava.
HV = Hepatic vein.
PV = Portal vein.
SHVC = Suprahepatic vena cava.

TABLE 5. *Associated Injuries in 31 Patients*

Injury	No. of Patients
Liver	31
Diaphragm	13
Lung	10
Extremity	5
Stomach	3
Small bowel	3
Colon, spleen, renal vein, brain	2 each
Aorta, renal artery, esophagus, spinal cord	1 each

patients had midline abdominal incisions followed by extension with a median sternotomy.

Injuries for which the shunt was placed are listed in Table 4. Twenty-three patients (74%) had injuries to the inferior vena cava, whereas the hepatic veins were involved in 13 patients (42%). One patient, no. 22, had an intrahepatic portal vein injury that was not controlled with the initial Pringle maneuver as evidenced by persistent hemorrhage from beneath the porta hepatis. Two patients with devastating injuries exsanguinated as the shunt was being placed and did not have the extent of their juxtahepatic vascular injuries delineated.



FIGS. 1A and B. *A*. Properly positioned atriocaval shunt fashioned from a chest tube. *B*. Atrial purse string suture and incision in atrial appendage.

Associated injuries are listed in Table 5. All patients in the series had hepatic injuries. In 13 patients (42%), the injury to the hepatic parenchyma was judged to be severe, *i.e.*, life-threatening in its own right. One patient had a severe pulmonary hilar injury requiring pneumonectomy. Another patient had an aortic injury at the level of the diaphragm severe enough to require prosthetic graft replacement. Two patients had severe intracranial injuries.

Aortic clamping was used to maintain perfusion to the coronary and cerebral circulation in 25 patients (81%). All 13 patients with resuscitative thoracotomy had the thoracic aorta clamped. Ten of the 12 nonsurvivors (83%) without resuscitative thoracotomy, and two of the six survivors (33%) had the aorta clamped at the diaphragm.

The device most often used for vascular isolation was a 36 French chest tube. The shunt was usually inserted through the right atrial appendage and secured at the intrapericardial vena cava and suprarenal vena cava with Rumel tourniquets (umbilical tape snares) (Fig. 1). In seven patients, the size of the shunt was not stated, and in one patient, a 28 French chest tube was used. An additional hole, approximately the size of the internal diameter of the chest tube, was cut 20 c from the closest of the drainage holes. In three patients the shunt was placed through a venotomy in the infrarenal vena cava and secured in the same fashion as those inserted through the atrium. In the most recent patient, difficulties encountered in surrounding the suprarenal vena cava resulted in the use of a 9-mm internal diameter plastic endotracheal tube with omission of the lower tourniquet (Fig. 2).

The shunt was successfully placed in 27 of 31 patients (87%). Four patients were exsanguinated as a result of their injuries while the shunt was being secured. Despite the successful placement of the shunt in 27 patients, only 15 patients (48%) lived long enough to have their injuries repaired.

Eleven patients had hepatic resections performed. There were nine anatomic lobectomies (one for exposure of a retrohepatic vena caval injury only) and one left lateral segmentectomy. In patient no. 14, the entire liver was avulsed from the vena cava and hepatic pedicle. After placement of the atriocaval shunt, the liver was lifted from the abdomen for bench repair of vascular injuries; however, the patient died before reimplantation could be performed. In the patient with the isolated portal vein injury (Table 2), the lobectomy was performed at a reoperation for hepatic necrosis and not during the previous procedure for hemorrhage when the shunt was used.

Results

Twenty-five patients (81%) died of their injuries. Of the 25 nonsurvivors, 21 (84%) exsanguinated in the operating room. Four patients who ultimately died left the operating room alive. Two had persistent hemorrhage after repair of their vascular injuries. Patient no. 16 continued to bleed while in the intensive care unit and died of shock and exsanguination. Patient no. 23 initially had successful control of hemorrhage but developed recurrent bleeding a few hours after the original operation. This patient was taken back to the operating room at which time the bleeding was noted to originate from severe bilobar hepatic injuries. He subsequently died in the operating room. Patient no. 25 died of refractory shock 12 hours after surgery despite successful repairs. This patient was 64 years old and had injuries to both the suprahepatic vena cava and the posterior aspect of the intrapericardial vena cava. Patient no. 22 died of multisystem failure and sepsis on the sixth postoperative day.

Unlike previous series,[11] the number of associated injuries, *per se*, did not adversely influence mortality rate. The average number of associated injuries for survivors in this study was 3.3, and the average number of associated injuries for nonsurvivors was 2.5. In contradistinction to the number of associated injuries, the severity of individual associated injuries did affect outcome. All patients with severe hepatic parenchymal injuries and those treated with hepatic resection died. In one of these cases, the patient did not have a severe hepatic injury, but the resection was performed to expose a stab wound in the retrohepatic vena cava. Two patients had severe intracranial injuries that were not likely to be compatible with survival. The patient with the suprarenal aortic injury also did not survive.

The mechanism of injury did influence survival, although not as anticipated. All patients sustaining stab wounds and blunt trauma died. The reason for the deaths in those patients with stab wounds is most likely related to their condition on arrival to the hospital. In three patients, resuscitative thoracotomy was required. The remaining three were in shock on arrival, and two were treated by hepatic resection. It is possible that the added blood loss associated with hepatic resection may have affected the outcome of these latter cases.

The patient's condition on admission to the emergency center correlated with survival. All patient's requiring resuscitative thoracotomy died. Furthermore, all patients who died were in shock on admission. Twenty-three of the 25 patients (92%) who required aortic clamping died. Technical problems with the use of the shunt occurred in seven patients (Table 6). The majority were related to delays in decision making or difficulties encountered in placement of the lower Rumel tourniquet. All seven of these patients died.

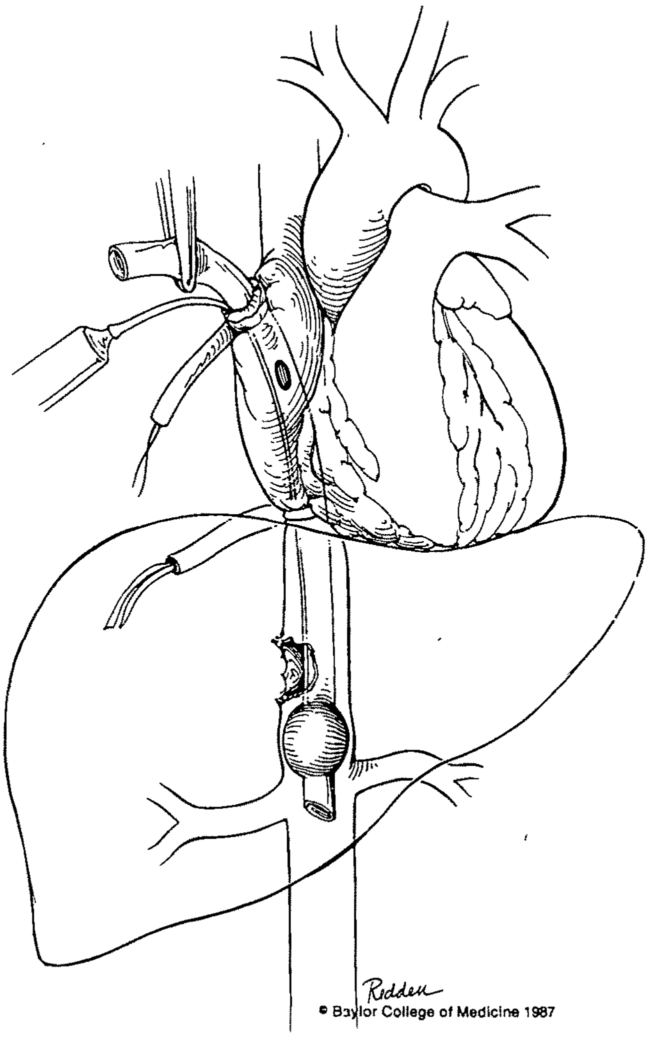


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FIG. 2. Properly positioned atriocaval shunt fashioned from an endotrachael tube. Modified from Yellin AE. Arch Surg 1971; 102:566–573.

Six patients (19%) survived and were discharged from the hospital in satisfactory condition. The survivors had several characteristics in common. Each sustained a

TABLE 6. *Technical Difficulties with the Use of the Shunt in Seven Patients*

Problem	No. of Patients
Late placement	3
Lower tourniquet below renal veins	2
Injury to SRVC during tourniquet placement	2
Atrial drainage hole too close to chest tube fenestrations	1
Total	8*

* One patient with the tourniquet below the renal veins also had an iatrogenic injury to the SRVC.

SRVC = Suprarenal vena cava.

TABLE 7. *Postoperative Complications in Six Survivors*

Complication	No. of Patients
Abscess	
Intra-abdominal	3
Intrahepatic	1
Respiratory failure	3
Postoperative hemorrhage	2
Colocutaneous fistula	1
Small bowel obstruction	1

gunshot wound that injured the retrohepatic vena cava. No survivors required either resuscitative thoracotomy or hepatic resection. Of the three survivors who were in shock on admission, two were operated on within 15 minutes of their arrival. The three patients who were not in shock on admission survived.

Four of the six survivors had serious postoperative complications (Table 7). Three patients had intra-abdominal abscesses that required surgical drainage. In one patient, a colocutaneous fistula developed several weeks after drainage of an intra-abdominal abscess. This patient ultimately required treatment with proximal fecal diversion. One patient, no. 29, in whom an intrahepatic abscess developed, had an anterior defect in the retrohepatic vena cava tamponaded by approximating the hepatic parenchyma over the vascular injury. This was done after a successful suture repair of a posterior hole in the retrohepatic vena cava to avoid extensive hepatic dissection. The intrahepatic abscess was treated satisfactorily by percutaneous drainage. Three patients had respiratory failure and required prolonged endotracheal intubation and ventilation. Two patients had postoperative hemorrhage and required prompt reoperation. One patient had a partial small bowel obstruction that was treated conservatively. Only a single survivor had an uncomplicated recovery. The length of hospital stay for survivors ranged from 11 to 198 days with an alarming average of 71 days. No survivors had long-term sequelae as a result of the shunt.

Discussion

The first clinical use of the atriocaval shunt was by Shrock et al. in 1968.[1] From dissections of human cadavers, they made the observation that there were no venous tributaries other than the hepatic veins, right adrenal vein, and inferior phrenic veins that entered the inferior vena cava above the level of the renal veins. With this vital information, they devised a technique for maintaining venous return from the renal veins and the infrarenal vena cava to the right atrium, and producing a relatively bloodless field with the addition of a Pringle maneuver. They reported the use of this technique in a child who sustained blunt trauma to the liver with injury to the hepatic vein. Although the child did not survive, the report stimulated great interest in other major trauma centers. Bricker and co-workers, from this institution, reported the first patient to survive a repair of injuries to the hepatic vein and retrohepatic vena cava with the use of the atriocaval shunt in 1970.[12] One year later, Bricker et al. reported a second survivor whose extensive injury to the retrohepatic vena cava was also treated with the atriocaval shunt.[2] Other successful cases were reported by Brown et al.,[13] Yellin et al.,[3] Fullen et al.,[4] and Turpin et al.[5] These early successes added enthusiam for the use of the shunt; however, as Walt pointed out by in 1978, not everyone had been able to achieve the results reported by others.[6] Kudsk et al. reported a decade of experience with this technique at San Francisco General Hospital in 1982.[11] The shunt was placed in 18 injured patients, and there were four long-term survivors. One additional patient lived for 45 days. Despite this cautiously optimistic report, pessimism still remained. In 1986, Pachter et al. reported six consecutive patients with juxtahepatic venous injuries managed without the shunt, and five of the six survived.[9] He clearly demonstrated that the use of the atriocaval shunt was not a prerequisite for the successful management of all patients with these injuries.

Until recently, reports of patients surviving blunt trauma requiring the atriocaval shunt have been rare.[14] In 1987, Rovito published a remarkable series in which four of nine patients sustaining blunt trauma to the liver or juxtahepatic veins survived after treatment with the atriocaval shunt.[15] It was this report, to a large extent, that stimulated an interest in reviewing our own techniques and results.

Evaluation of the Current Series

There is no question that the mortality rate for injuries to the retrohepatic vena cava, suprahepatic vena cava, and hepatic veins, despite the aggressive use of the atriocaval shunt, remains exceptionally high. In view of Pachter's superb results in managing these injuries without the shunt, one is forced to ask the question as to whether the atriocaval shunt was responsible for the high mortality rate in the current series. Several observations make that conclusion unlikely. The fact that 42% of the patients in this series required resuscitative thoracotomy suggests that prehospital or preoperative blood loss and shock are major contributing factors. Survival rates for patients sustaining either blunt or penetrating abdominal trauma requiring resuscitative thoracotomy at this institution have usually been in the range of 3%.[10] If these patients are excluded from survival statistics, then six of 18 patients (33%) would have survived. Nevertheless, the mortality rate still remains high even when resuscitative thoracotomy is not required.

In the past, prehospital delay has been cited as being in part responsible for the significant mortality associated with injuries to the vena cava.[16] It was believed that these delays resulted in a large percentage of patients presenting to the hospital in shock. During the current study, the average prehospital delay dropped from 40 minutes to 25 minutes; at the same time the percentage of patients with vena caval injuries presenting in shock rose from 44% to 55%. This implies that more patients with severe hemorrhage and shock are reaching the hospital alive than before, an obvious characteristic of this series. This conclusion is further supported by operative observations from the three groups of patients in Tables 1, 2, and 3. The most critically ill, those requiring resuscitative thoracotomy, had on the average a lower pH, lower core temperatures, shorter operations, and less blood administered than did those who died but did not require resuscitative thoracotomy, or the survivors (Table 8). The same statement also can be made in comparing the latter two groups. This strongly suggests that nonsurvivors died so precipitously from pre-existing shock and hemorrhage that they did not live long enough to be given as much blood during the operation as did the survivors. A technique for gaining hemostasis would be most unlikely to produce this result.

Another factor that may bias these results is the fact that not all juxtahepatic vascular injuries treated at this institution have required the use of a shunt. During the study period, 15 additional patients were treated for injuries to the retrohepatic vena cava without an atriocaval shunt. Seven of the 15 patients survived. The overall survival rate for all patients sustaining retrohepatic vena caval injuries during the study period was 37%. Similar data are not available for patients with hepatic venous injuries because many of these patients are treated with more conservative techniques such as parenchymal suture.[17] The use of the shunt at this institution is reserved for patients with more severe injuries who cannot be treated using simpler techniques. Finally, there were no instances in this series where the application of the atriocaval shunt was believed to be directly or in part responsible for any deaths. Therefore, in the opinion of the authors, it was the extent of the patient's injuries, the rate of their hemorrhage, and the severity of their shock that resulted in a high mortality rate rather than the use of the atriocaval shunt.

Decision Making

Recognizing the need to use the atriocaval shunt is not always easy. This can lead to disastrous delays as massive blood loss continues. The following operative findings imply that the shunt may be needed. With secure occlusion of the hepatic pedicle (Pringle manuever), profuse venous hemorrhage: (1) from the posterior aspect of the right lobe of the liver, usually through the caudate lobe; (2) into the lesser sac in the absence of a portal venous injury; (3) at the diaphragm anteriorly; (4) from deep within the hepatic parenchyma; or (5) from beneath the porta hepatis indicates that injury to the retrohepatic vena cava, suprahepatic vena cava, or the hepatic veins exists. Unusual presentations may also occur, including hemorrhage into the right hemithorax and pericardial tamponade.

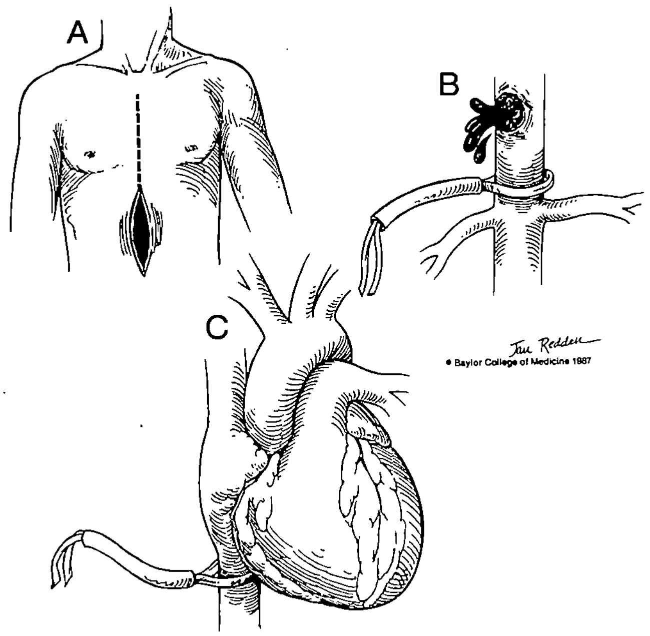
TABLE 8. *Intraoperative Averages of Physiologic Parameters, Length of Operation, and Red Blood Cell Replacement in 31 Patients According to Preoperative Status and Outcome*

Preoperative Status and Outcome	Lowest pH	Lowest Temperature (C)	Length of Operation (hours)	RBC Units Given
Resuscitative thoracotomy and died (N = 13)	7.03	31.2	1.2	18.4
Without resuscitative thoracotomy and died (N = 12)	7.11	31.6	1.9	27
Survived (N = 6)	7.23	32.6	4.9	30

The surgeon should attempt to palpate the region of the injury to determine the size of the defect. Excessive time should not be spent in this endeavor as significant blood loss may continue. If the lesion is palpable and small, it may be prudent to continue dissection to expose the defect and repair it without a shunt. If the defect is large (greater than 1.0–2.0 cm in diameter) the use of the atriocaval shunt is highly desirable unless clamp control can be easily achieved.

The importance of the Pringle maneuver cannot be overemphasized. Not only does this technique control blood loss, it also plays a pivotal role in decision making. Obviously, if the hemorrhage is controlled with a Pringle maneuver, a shunt is not necessary.

Even with the best intentions, pernicious delay may occur. This can result from difficultly in making a diagnosis or from inexperience and a reluctance to expand the scope of the operation. This is understandable since injuries requiring the atriocaval shunt are rare. During the study period, 268 vena caval injuries were treated, and only 9% required the use of the shunt. Furthermore, during the same period, 1782 hepatic injuries were treated, and the shunt was required in only 1.8% of these cases. The decision to place the shunt, with the subsequent finding that it may not have been necessary, should not be harshly criticized.



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FIGS. 3A–C. *A.* Preferred thoracic incision for patients not requiring resuscitative thoracotomy. *B.* Proper position for lower tourniquet is around suprarenal vena cava in abdomen. *C.* Proper position for upper tourniquet is around intrapericardial inferior vena cava.

Maintaining hemostasis, before and during placement of the shunt, is crucial to survival. In most cases, particularly those associated with severe hepatic injuries, posterior compression of the liver with laparotomy pads in addition to a Pringle manuever will be satisfactory.

Adequate exposure is also mandatory. In patients who have not required emergency thoracotomy, extension of the midline abdominal incision into a complete median sternotomy affords ideal exposure. Radial division of the diaphragm to the adventitia of the inferior vena cava is often necessary. Great care must be taken when completing this incision because the tough diaphragmatic fascia at the vena caval hiatus yields suddenly to expose the delicate inferior vena cava beneath. For patients with initial anterolateral thoracotomy, division of the lower portion of the sternum will also facilitate exposure although closure may be awkward. Achieving adequate exposure and maintaining hemostasis are not always compatible. This is especially true when attempting to surround the suprarenal vena cava for placement of a Rumel tourniquet. Posterior compression of the liver increases the difficulty of exposing the suprarenal vena cava. This dilemma has led to minor injuries of the suprarenal vena cava that required repair in two patients in the current series.

Once the decision has been made to use the atriocaval shunt, many options regarding size, style, and route of insertion are available. The ideal size of the shunt has yet to be determined. It should be large enough to permit adequate venous flow under low pressure conditions and yet not so large as to be cumbersome. Thirty-six French chest tubes were often used in this series, although smaller ones have been successfully used. The advantages of chest tubes are their availability and flexibility. They can be inserted from either the atrial or vena caval approach and are available at all times and in all hospitals. The main disadvantage of the chest tube is the need to control the suprarenal vena cava with a Rumel tourniquet. Cannulation through the right atrial appendage is preferable since this is a readily accessible and easily controlled route with the aid of the curved Glover or Satinsky clamp (Fig. 1 inset). Cannulation of the infrarenal vena cava may be desirable for surgeons uncomfortable with atrial cannulation or in patients with an existing anterolateral thoracotomy because the external end of the shunt may rub annoyingly against the exposed upper costal margin.

Their are two styles of shunts: straight tubes and those with inflatable balloons at one end or both. Specially constructed balloon tipped shunts have been used experimentally[18,19] and clinically.[8,20,21] These catheters, depending on design, may be inserted from either only the atrial or infrarenal approach. Two balloon shunts were designed for insertion *via* the femoral vein.[20,21] This approach offers the advantage of not requiring an incision in a large venous structure, but suffers from the drawback of requiring an additional incision and dissection. A potential shortcoming of special devices that are seldomly used is that they may be difficult to find expeditiously in a large operating room suite. The use of an endotracheal tube, first described by Yellin et al.,[3] and used so successfully by Rovito,[15] is an attractive alternative. It is instantly available from the anesthesiologist and comes sterilely packaged.

Technique

The atriocaval shunt increases the complexity of the operation, and critical maneuvers must occur simultaneously. It is essential that a single individual direct these operations. A median sternotomy is the perferred thoracic incision (Fig. 3A). The control of hemorrhage with posterior compression of the liver and a Pringle maneuver is vital and must be performed as soon as the diagnosis is suspected. This will enable the anesthesiologist to correct existing volume deficits and metabolic derrangements before proceeding. It may be desirable at this point to remove previously applied aortic clamps or at least move them to below the level of the renal arteries.

The next step is to prepare the shunt. For chest tubes, a hole is cut 20 cm from the nearest drainage hole. If an endotracheal tube is used, the distance should be somewhat less, 17–18 cm from the nearest hole past the balloon. Care must be taken not to damage the inflation lumen of the balloon.

The end of the shunt that will be outside of the heart or vena cava is securely clamped. Although many have made the recommendation to use this end as an intravenous infusion site, adaptors may be difficult to find and the technique adds unnecessary complexity. Also, complications such as air embolism may occur. Control of the suprarenal vena cava with a Rumel tourniquet should be obtained (Fig. 3B). This treacherous step is omitted if a transatrial endotracheal tube is used. Next, a Rumel tourniquet is placed around the intrapericardial inferior vena cava (Fig. 3C). A partially occluding clamp is then applied on either the right atrial appendage or infrarenal vena cava and a purse string suture is placed. After making an incision encompassed by the purse string, the clamp is removed and the tube is inserted and directed toward the liver. When passing the tube from above, care must be taken not to insert the shunt into the hepatic or renal veins. The surgeon controlling the operation should palpate the retrohepatic vena cava and guide the tube into the correct location. The purse string should then be secured with a Rumel tourniquet and all tourniquets secured or balloons inflated. The position of the shunt should be evaluated by palpation above and below both Rumel tourniquets to ensure that all the holes in the shunt are outside of the area of vascular isolation.

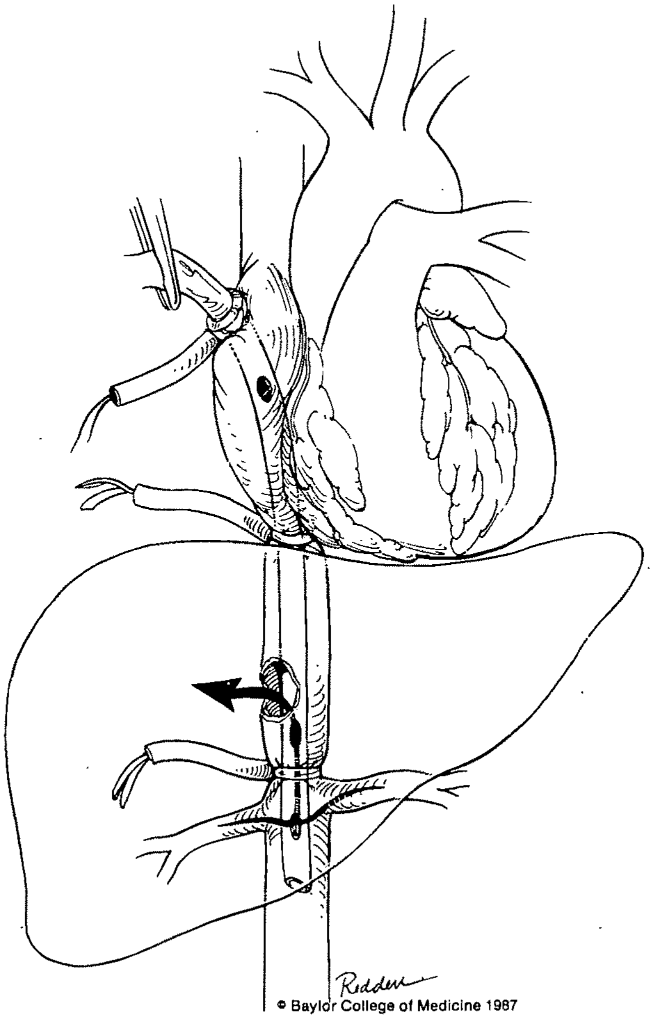

FIG. 4. If chest tube is positioned so that not all holes are below the lower tourniquet, persistent hemorrhage from the venous injury will occur.

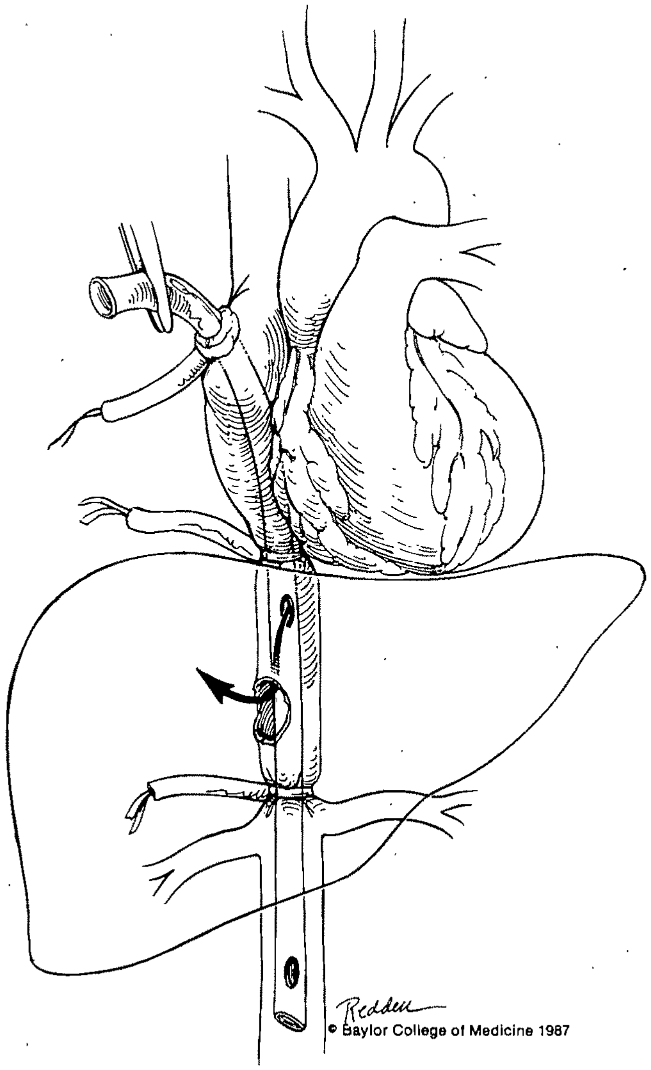

FIG. 5. If atrial drainage hole is positioned below the intrapericardial tourniquet, hemorrhage will continue and venous drainage from the lower body will not reach the heart.

Due to the fact that the hepatic veins and isolated segment of the vena cava may drain residual blood, and that the right adrenal vein, inferior phrenic veins, and perhaps aberrant tributaries may be within the area of vascular isolation, some bleeding usually persists from the vascular injury. The amount of blood loss that occurs, although potentially significant, is trivial com-

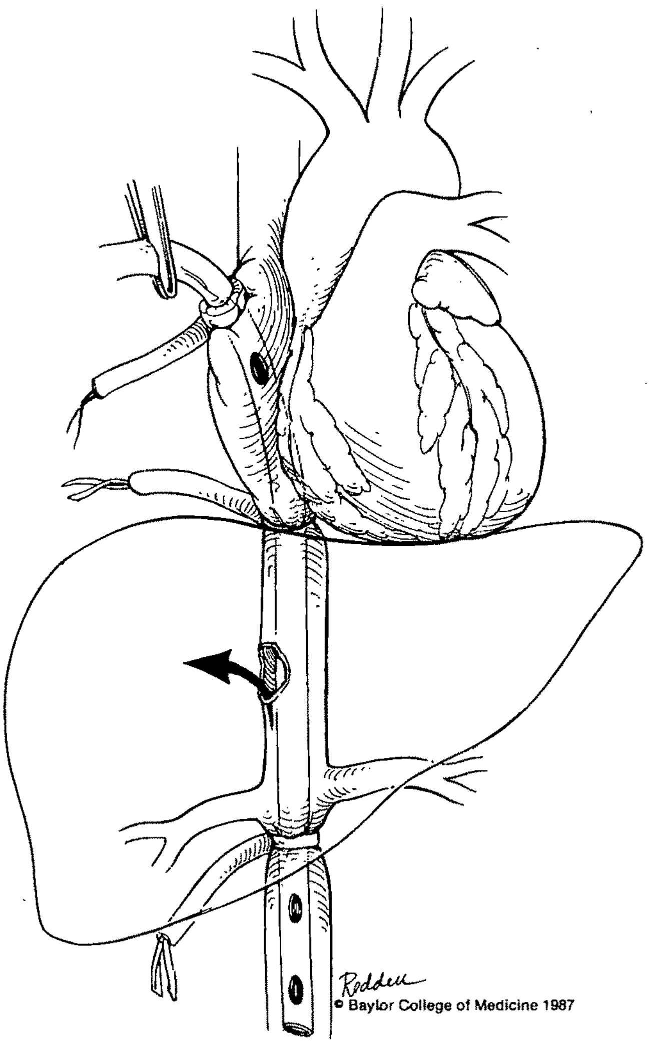

FIG. 6. If lower tourniquet is positioned below the renal veins, vascular isolation does not exist.

pared with the torrential hemorrhage seen from uncontrolled injuries of the large veins.

Technical Pitfalls

Despite the apparent simplicity of the technique, many problems with the use of the shunt can be encountered. If the initial hole in the chest tube is too close to the drainage holes, one of the fenestrations of the chest tube or the atrial drainage hole will be between the Rumel tourniquets, resulting in persistent massive hemorrhage from the site of the injury (Figs. 4 and 5). The only solution to this problem is to withdraw the shunt and correctly prepare another one. If the lower Rumel tourniquet is placed below the renal veins, vascular isolation will not exist (Fig. 6). Injury to the suprarenal vena cava may occur during attempts to surround it when exposure of the area is difficult. Excessive traction on the suprarenal vena cava may cause tearing of the lumbar veins at the origins of the renal veins. During insertion, the shunt may engage a laceration of the retrohepatic vena cava or suprahepatic vena cava causing additional damage (Fig. 7). If the vascular isolation achieved is perfect, a rare circumstance indeed, it is possible that a considerable amount of air may enter the hepatic veins and isolated vena caval segment. When this occurs, the lower Rumel tourniquet or Pringle maneuver should be released before completing the vascular suture line to ensure evacuation of the air.

The Pringle maneuver may be inadequately applied or become dislodged during required manipulations, and significant bleeding will persist. Another potential reason for failure of the Pringle maneuver is the existence of accessory or aberrant left hepatic arteries in about 25% of patients. These may not be included in the usual manuever. If inadequate hemostasis is encountered despite a well-positioned shunt and a secure Pringle maneuver, this possibility should be considered.

Alternatives and Controversies

The significant mortality rate associated with juxtahepatic vascular injuries treated with the atriocaval

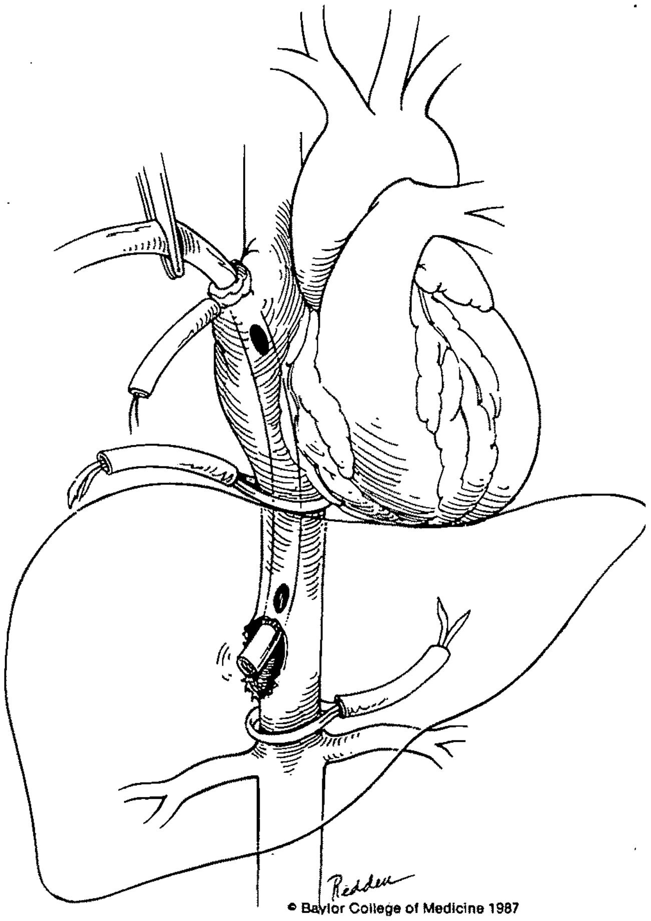

FIG. 7. During insertion, the surgeon should direct the shunt into the proper position and prevent the shunt from extending the venous injury.

shunt has provided a stimulus to find alternative techniques. One option is to use the hepatic parenchyma with intact capsule to tamponade the low pressure venous bleeding. This was successfully used in one patient in this series who would have otherwise required division of the liver to the level of the vena cava. This is not a unique recommendation, and others have used this method with success.[22] This technique is ideally suited for wounds where there is little destruction of the hepatic parenchyma. Great care must be taken in placing the sutures accurately and tying them gently. Another option is to achieve vascular isolation with occluding clamps on the vena cava above and below the liver after applying a Pringle maneuver and a clamp on the aorta. This concept was initially described by Heaney et al. and used by them in elective cases of hepatic resection.[23] The same approach has also been used for the treatment of trauma to the juxtahepatic vasculature in children.[24] In a similar fashion, occlusive balloon catheters have been used both experimentally,[25,26] and clinically.[2,26] Unfortunately, it has been our experience, as well as that of others,[3] that severely injured patients with significant hemorrhage and shock do not tolerate occlusive vascular isolation well.

Another alternative, appropriate for small injuries of the suprahepatic vena cava or retrohepatic vena cava that can be controlled with a finger, is to sew beneath the finger with a needle large enough to make the pass with one motion, and then apply gentle traction to the suture to aid in hemostasis. The remainder of the suture line is then completed while accepting the blood loss. Minor injuries of the retrohepatic vena cava exiting through or posterior to the caudate lobe may be controlled by dividing the left or right triangular ligament and rotating the lobe to the midline. Lobar rotation will aid in exposure of the injury as well as partially or completely occluding the retrohepatic vena cava. Patients may not tolerate this maneuver well, but if the injury is small, it may be the most expeditious way to control hemorrhage and repair the injury. In unusual circumstances, injuries may be exposed enough to grasp with a thumb forceps and secure with a partially occluding clamp.

A unique and bold approach is that of Pachter and co-workers.[9] After expressing disappointment of having only two of four survivors with the shunt, they developed a direct transhepatic approach. The essentials of this technique include: (1) the maintenance of posterior compression of the liver for hemostasis while correcting volume deficits; (2) the use of a Pringle maneuver for as long as is required to repair the injury; and (3) division of as much liver as is necessary, using finger fracture, to expose the injury and gain direct control. In a remarkable series of 10 patients with juxtahepatic vascular injuries, the first four were managed with a shunt and two survived. The next six consecutive patients were managed without a shunt and five of the six survived. The authors agree heartily with Pachter's emphasis on restoring lost volume, maintaining hemostasis, and an adequate duration of the Pringle manuever; however, this achievement may be a greater tribute to the skill of the surgeons involved than testimonial to the technique.

Conclusions

Extensive injuries to the juxtahepatic veins remain lethal injuries. The high mortality rate is due to profuse hemorrhage and severe shock produced by these injuries before the time vascular control can be attempted. The atriocaval shunt is not a perfect solution to the problem and difficulties with its use may occur; however, when the decision to use the shunt is made rapidly and hemostasis is maintained with vigilance, patients with otherwise irreparable injuries may survive. Hepatic resection should be assiduously avoided, and is not necessary only for exposure of the injury. Alternative shunting techniques, *e.g.*, use of a transatrial endotracheal tube, may help to overcome technical problems and improve survival in the future.

Acknowledgment

We thank Marian Torres for her invaluable technical assistance and clerical help.

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DISCUSSION

DR. J. DAVID RICHARDSON (Louisville, Kentucky): This paper represents another excellent contribution and presentation from the Houston group on the management of a difficult topic in trauma, and I certainly would recommend the manuscript by Drs. Feliciano, Burch, and Mattox to your attention. They have done an excellent job of outlining some of the real pitfalls that these patients present.

At issue is whether or not the atriocaval shunt is really necessary for juxtahepatic caval injuries or whether these injuries really could be repaired with similar results without the use of a shunt. With the use of an atriocaval shunt, we have treated 24 patients with retrohepatic or juxtahepatic caval injuries at the University of Louisville. Unlike the Houston group, 16 of our cases were due to blunt trauma, and only six were due to penetrating trauma.

Seven of these 24 patients were able to leave the operating suite alive. Three subsequently died of sepsis, coagulopathy or various other problems, and there were four long-term survivors. These results are not altogether dissimilar from those presented from Houston. Two of the four survivors had blunt trauma unlike the Houston group's series and two of our patients had penetrating injuries. In two of these cases in which I personally participated, the caval injuries were fairly small, and quite honestly, they could possibly have been repaired by direct suture technique or conventional techniques without the use of a shunt. However, I agree with the point the authors made, that is, once these injuries are recognized, you need to commit fairly promptly to either using the shunt or not, and we did choose that technique with success.

We have come to believe that prompt placement of the shunt, as has been indicated by the authors, before the development of coagulopathy is the key to its successful use, and, therefore, we try to move forward with prompt shunt placement as soon as we recognize the severely bleeding venous injury in the retrohepatic position that does not promptly respond to a Pringle maneuver.

Technically, we have found the endotracheal tube to be useful in that it obviates the need to encircle the inferior vena cava with its attendant technical complications. I think it is maybe a little bit tougher to cut that more proximal hole, but at least you don't have to deal with the distal cava in quite the same manner.

In our residency program, we have made liberal use of the fresh dissection lab which we developed in conjunction with the department of anatomy, and I think, quite simply, if you are going to try to teach residents to do that, you really can't do it with a bleeding, dying patient, and that the forethought of having gone through this a couple of times in the dissection lab is certainly one that I would commend to those of you who are involved in resident education or who might be an occasional operator in this area yourself.

In summary, we believe that the atriocaval shunt does have a place in these most difficult injuries, but that the very nature of the injuries themselves will always make the survival ability of these patients lower than would ordinarily be satisfactory. We will continue to use the shunt in these selected patients, however.

DR. LEON PACHTER (New York, New York): I would like to congratulate the Baylor group on their superb contribution to the management of juxta hepatic venous injuries employing an atriocaval shunt.

A recent review of 66 cases treated at major trauma centers in which atriocaval shunts were used revealed that only 15 patients survived for a mortality of 77%.

The authors were able to salvage 6 of 18 patients for a mortality of 67%, when patients with resuscitative thoracotomy were excluded. The lethal nature of this injury is quite evident.

Why has the mortality with atriocaval shunting been so high? First and foremost is the devastating nature of the injury itself, but in most series, failure of the atriocaval shunt was probably related to three key factors. First, delay in early recognition of the injury. Second, delay in shunt-insertion until all other methods have been exhausted to control hemorrhage. At this point, a coagulopathy exists and no matter what the surgeon does, the patient will most probably die. To insert a shunt at this time only will result in a bad name for the procedure. Three, lack of experienced personnel for expeditious shunt insertion. If these three factors are avoided as they were by the authors, then the devastating nature of the injury itself must be implicated as the eventual cause of death.

Given this fact, what then is the optimal method of managing these injuries? Atriocaval shunting no doubt will be the method of choice, but alternatives do exist.

We managed six consecutive patients at Bellevue Hospital without a shunt, employing the technique of prolonged portal triad occlusion up to 60 minutes and rapid finger fracture of normal hepatic parenchyma to get down to the site of vascular injury for primary repair. Five patients survived.

Clearly, there exists a group of patients that can be managed without a shunt.

In their manuscript, the authors themselves report 15 patients with retrohepatic caval injuries who were managed without a shunt. Seven of the 15 survived for a salvage rate of nearly 50%. The survival in this group of patients without a shunt is clearly somewhat better than the 67% reported in patients in whom a shunt was used.

I would appreciate the authors' commenting on the two groups and elucidating for us the criteria for either using an atriocaval shunt or not.

As no one institution has enough patients for statistically significant data, a larger series will be needed to set up guidelines as to which patients require a shunt and which patient can be managed without it.

I enjoyed the manuscript, and I am sure that it will be a landmark paper in the field of hepatic trauma.

DR. JOHN OCHSNER (New Orleans, Louisiana): Dr. Feliciano has shown us that this is really a devastating lesion, having an 81% mortality.

When I was a boy some 30 years ago in Houston, we researched our inferior vena cava injuries, and we had 48 inferior vena cava injuries. There were four patients with retrohepatic vena cava injuries. All four patients died, but two of them were not bleeding actively at the time of exploratory surgery, and it wasn't until we entered the hematoma that we got into the bleeding problem.

We suggested at that time that these areas be packed in an attempt to let this clot and to maintain an intact retroperitoneal space. In order to test this hypothesis, we went to the lab.

(Slide) We took a Himelstein valvulotome, inserted it through the common femoral vein of a dog, brought it up into the retroperitoneal space at the level above the renal veins, and this cut out an elliptical piece of vein and adjacent tissue. The instrument cuts out a section in the posterior aspect, leaving the peritoneum intact. (Slide) You can see the hemorrhage begin.

(Slide) Shortly thereafter, you see this massive hemorrhage. We did six dogs in this group. All of them survived. Then we sacrificed them a week later.

(Slide) And this is what you see: most of the blood has been absorbed. We opened the retroperitoneal space. (Slide) And one can see this elliptical incision of the vena cava that allowed the hemorrhage and yet allowed the clotting with the intact retroperitoneal space.

We then took another series of dogs to test whether we could make an incision into the inferior vena cava and then just make the retroperitoneal space intact. We did this by putting some buttress stitches as one sees here, taking a knife, a 15 blade, and incising the retroperitoneum and inferior vena cava. These buttress stitches are not into the cava but just into the peritoneum, and yet the retroperitoneum space controls the bleeding. Next, the dog is a sacrifice (Slide) a week later, showing a relatively small incision compared to the one in which a piece of tissue is taken with the valvulotone.

So we have pretty well proved that if one has an intact retroperitoneal space, with the low pressure in the hepatic veins and inferior vena cava at this level, one need not worry about the continued bleeding.

Now, since there was no evidence of duodenal injuries which would have required opening the retroperitoneal space I would like to ask the authors whether although there was a significant amount of concomitant injuries, could their patient have possibly been treated by allowing the retroperitoneal space to be maintained as an intact space?

Today with the advent of biological glue where we are able to control probably many of lacerations in the liver, I wonder if, in retrospect, Dr. Feliciano thought any of his patients could have been treated by a more conservative method of controlling the hemorrhage with tamponade.

DR. JOHN D. ASHMORE, JR. (Greenville, South Carolina): (Slide) That is a venacavogram made 6 weeks after a 23-year-old came in after turning his dune buggy over while racing.

As we opened the abdomen, it was obvious we had a serious hepatic injury, so without touching it, we went to a right thoraco-abdominal. He had avulsion of the retrohepatic cava, so we occluded above and below with clamps, and also used aortic occlusion at the diaphragm.

By the time we got through, we ended up putting in a 20 mm Dacron graft. It is about 4 cm long.

He, of course, had a rocky post-op course, but was discharged after about 4 weeks, and I had occasion to do a follow-up on him this summer.

He was admitted with a fractured pelvis. He was racing his speedboat and the throttle stuck. He said he had done 130 miles an hour, but down-home people tend to exaggerate. He, at least, fractured his pelvis when he did bail out of the boat.

I present this because there is still some question about Dacron grafts in the vena cava, and I did this cavogram in 6 weeks because in a series of dogs, just about all the grafts had some thrombi, and complete occlusion at 6 months. I was questioning whether or not he should be on chronic anti-coagulation. We did not anti-coagulate him, and as I say, he is still around 9 years later.

DR. ALFRED GERVIN (Richmond, Virginia): May I first congratulate Dr. Feliciano on his very nice presentation and thank him for providing me in advance with a copy of the 35-page manuscript.

The injury that the authors address, perforation of the retrohepatic portion of the IVC, is truly a dreaded situation in trauma, often leading to the demise of the patient and to the graying of the hair of even the most experienced trauma surgeon.

All surgeons have had some experience with this particular traumatic process, and I am delighted that we have before us today a rather extensive experience for review.

In this series from, the Ben Taub Hospital, there were 31 patients. Of all 31 patients, 11 were in full code arrest at the time of presentation to the emergency department and underwent the emergency department thoracotomy. All died.

Of the remaining 18 patients, six survived. If we closely scrutinize these survivors, several characteristics are evident. Number one, all had penetrating trauma.

At our institution we are one for twelve with caval shunting for patients with blunt trauma.

Number two, over one-half of your survivors were not in shock when they arrived in your emergency department. Therefore, these patients were in fairly good medical condition.

Number three, more than 70% of your patients had injuries only of the cava and not of the hepatic veins—perhaps a much less difficult injury to handle.

And four, no patient in your series with concomitant hepatic injury survived.

These data, therefore, motivate three questions.

Based on your experience (number one) should shunting even be attempted in patients who have undergone emergency room thoracotomy? Your mortality was 100%.

Number two, should shunting even be attempted in patients with concomitant major hepatic injury? Again, your mortality was 100%.

Number three, for these patients might not extensive abdominal packing provide a better chance for survival?

DR. ARTHUR J. DONOVAN (Los Angeles, California): Dr. Feliciano and his associates have importantly focused on the major unresolved problem and cause of mortality in hepatic trauma: hepatic vein and juxtahepatic venous injury. A number of years ago, we reported eight cases of such injury treated with a variety of techniques of vascular isolation: atrial shunt, infrarenal shunt, and multiple vascular occlusions as described by Heaney (*i.e.*, occlusion of the vena cava above and below the liver, a Pringle maneuver, and occlusion of the supraceliac aorta with a clamp or compression device). Four of the eight patients survived. Based on this clinical experience and the results of subsequent canine experiments, we concluded that multiple occlusive clamps were the preferable technique. We continue to believe that if vascular isolation is necessary, multiple occlusive clamps are the simpler technique and create a field that is dry enough for vascular repair. Aortic occlusion above the celiac axis is essential to prevent infradiaphragmatic flow when the suprahepatic cava is occluded.

Among 234 cases of hepatic trauma treated in the past 2 years, vascular isolation by multiple occlusive clamps was employed in four cases. This rate of vascular isolation is generally comparable to that reported by Dr. Feliciano. There were two survivors, one of whom underwent major hepatic resection. Despite resurgence of interest in packing, we are not convinced that it is effective in cases of the most severe hepatic vein and juxtahepatic venous injury. In closing, I would ask Dr. Feliciano to comment on whether he has utilized the technique of multiple occlusive clamps and on his experience with packing for major venous injuries. I fear that the nature of major hepatic vein and juxtahepatic venous injury is such that with currently available techniques, a continued high mortality will be experienced.

DR. JON M. BURCH (Closing discussion): Dr. Richardson, we have used the endotracheal tube in only a single case in this series. However, it does eliminate having to gain vascular control of the suprarenal vena cava, which, according to our experience, was a major source of technical difficulty. Avoiding this step may help improve results in the future.

We have also taken our residents to the dog lab and rehearsed the use of the shunt with them. I think that is an excellent suggestion for those of us with these facilities.

Dr. Pachter asked about the seven survivors with retrohepatic vena cava injuries who were mentioned in the study but in whom shunts were not used. In general, these patients had smaller injuries which usually could be occluded with a finger, were not as sick on admission, and did not require resuscitative thoracotomy with the frequency that those in our shunt series did. I am quite certain these are the reasons that those patients survived. It is also possible that the shunt might have benefited some of the patients in whom it was not used.

I agree completely with Dr. Ochsner's comments. Nonexpanding retrohepatic hematomas with an intact retroperitoneum ought to be considered similar to hematomas caused by blunt trauma to the kidney or pelvic bones, all of which are best left alone.

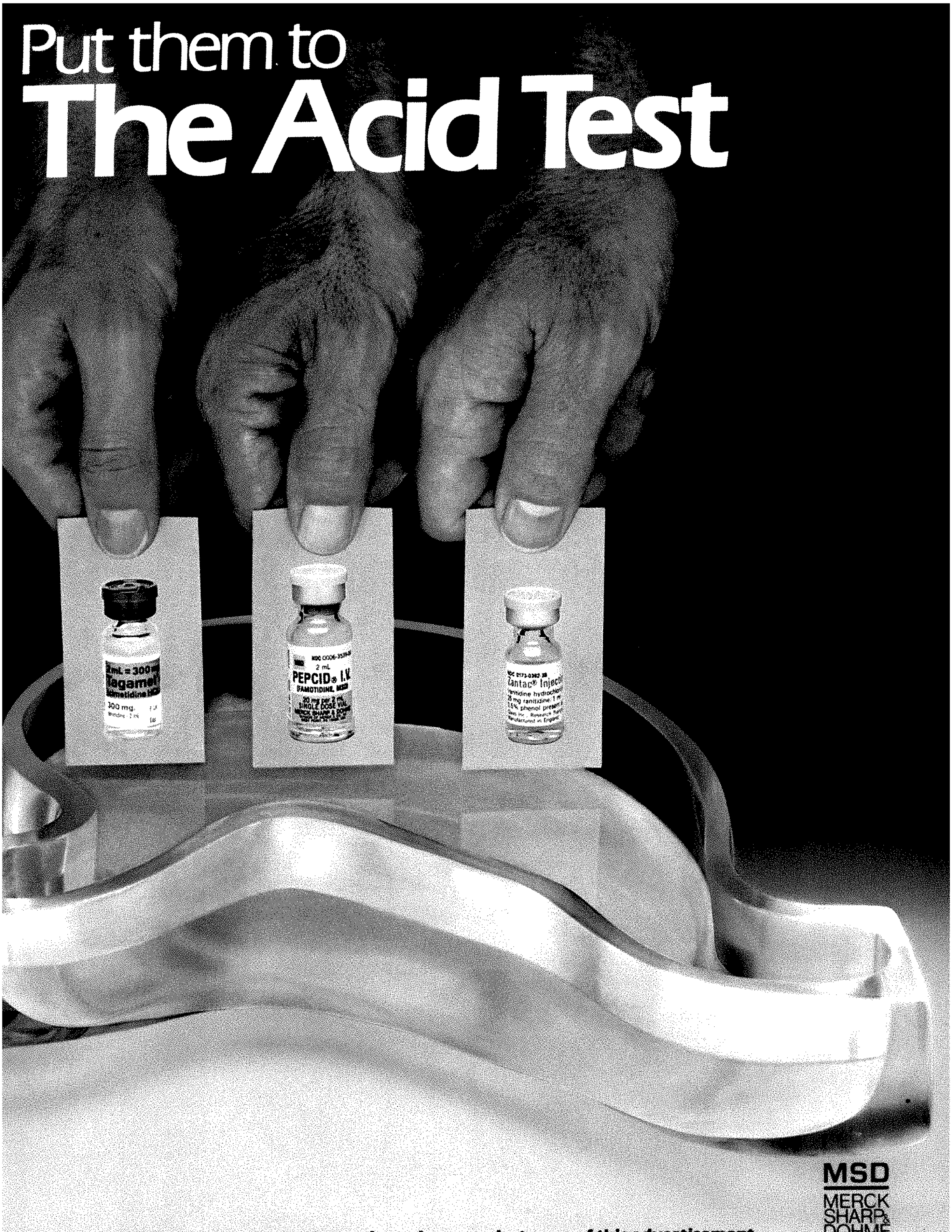
The senior author of this paper has venocavograms of two patients with penetrating injuries that show retrohepatic venous defects. One of these patients was not operated on and the other closed promptly after finding a small retrohepatic hematoma. Both patients survived.

Dr. Ashmore, we have not had to use a graft in the last 270 patients with vena caval injuries, but it is reassuring to see that patients can do well over a long period of time if such a graft is required.

Dr. Gervin, based on our experience, it is difficult to justify the use of a shunt in the circumstances you mentioned. However, this is a small series, and these injuries are always going to be rare. We have always operated under the supposition that unless we try to save such desperately ill patients, we will never succeed. Furthermore, for the individual patient who survives such an exotic injury, the survival rate is 100%. Therefore, we will persist in trying to use these techniques, including EC thoracotomy.

Packing is not an alternative to suture repair of large venous injuries. Our results, when that has been attempted, have been poor. These injuries must be repaired. Packing may be useful as an adjunct in patients who have coagulopathy, and was used successfully in one of the patients that Dr. Feliciano mentioned.

Dr. Donovan, I still marvel at the paper that you and Dr. Yellin wrote in 1971. We have tried the caval clamping technique which you have described. Our patients have not tolerated this procedure well. We have had the experience of trying this initially, with the patient experiencing cardiac arrhythmias and profound hypotension and having an unsuccessful outcome. Certainly there are patients who will tolerate this procedure, but we just don't know how to pick them, and that has been a source of great frustration.



For a Brief Summary of Prescribing Information, please see last page of this advertisement.

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Only one H_2 antagonist controls pH for up to 12 hours on a single dose

PEPCID® I.V. (Famotidine, MSD) is indicated in some hospitalized patients with pathological hypersecretory conditions or intractable ulcers or as an alternative to the oral dosage forms for short-term use in patients who are unable to take oral medication.

The recommended dosage is 20 mg q12h. Dosing intervals may need to be prolonged or dosage reduced in patients with severe renal insufficiency (creatinine clearance <10 mL/min) to adjust for the longer elimination half-life of famotidine. PEPCID I.V. is contraindicated in patients who are hypersensitive to any component of this medication. The adverse reactions reported for PEPCID Tablets may also occur with PEPCID I.V. In addition, transient irritation at the injection site has been observed with PEPCID I.V.

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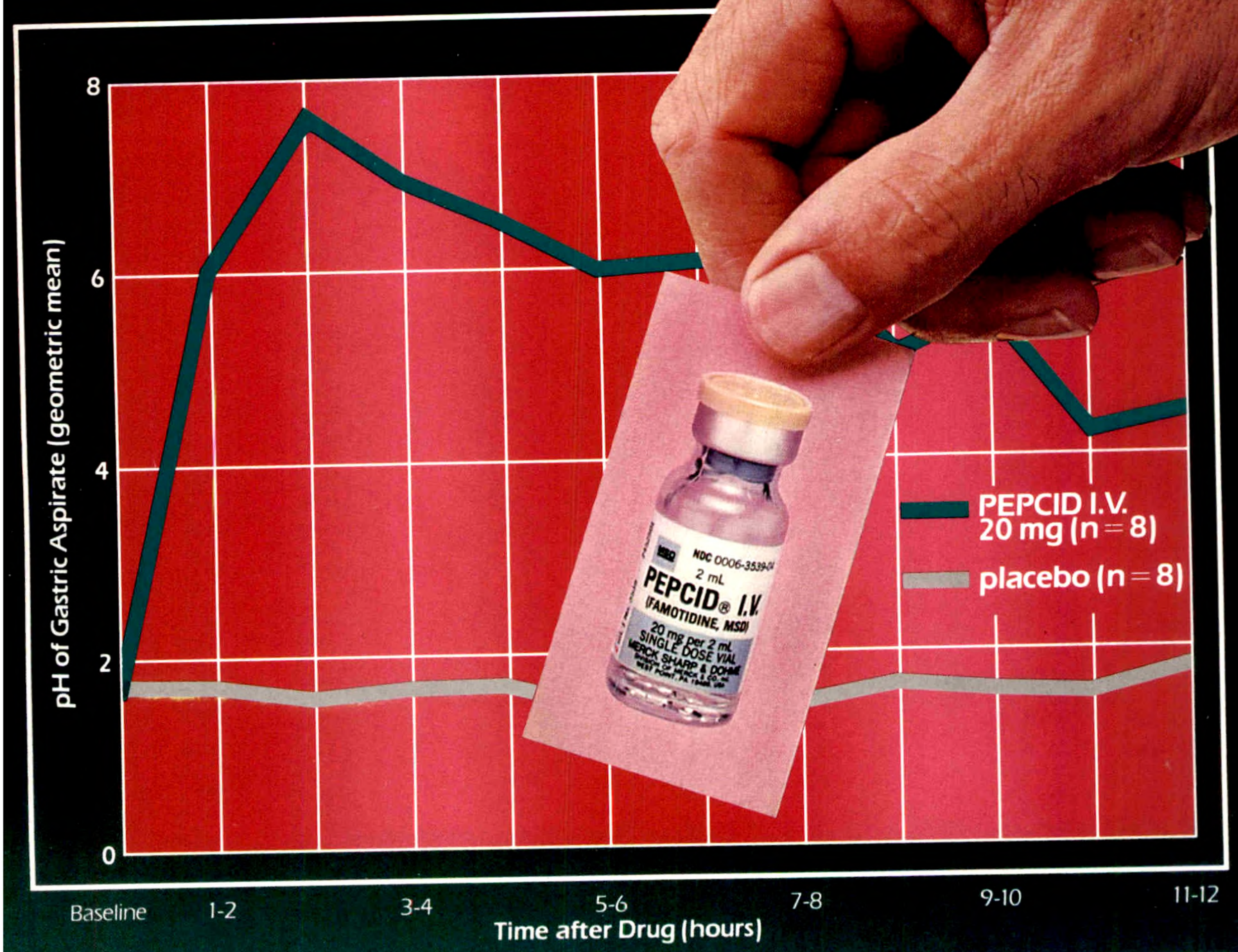

A double-blind, placebo-controlled study[1] involving eight volunteer hypersecretor subjects. The pH of gastric aspirates was measured hourly for 12 hours following single intravenous doses. PEPCID I.V. maintained the mean gastric pH above 4.0 at all time points throughout the 12-hour period with one 20-mg I.V. dose.

1. Ryan, J.R. et al.: Comparison of effects of oral and intravenous famotidine on inhibition of nocturnal gastric acid secretion, Am. J. Med. 81 (Suppl. 4B): 60-64, October 24, 1986.

INJECTION, 20 mg/2 mL

q12h Pepcid® IV

(Famotidine|MSD)

MSD
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SHARP&
DOHME

For a Brief Summary of Prescribing Information, please see following page.

TABLETS
Pepcid®
(Famotidine|MSD)
20 mg and 40 mg

ORAL SUSPENSION
Pepcid®
(Famotidine for Oral Suspension|MSD)
40 mg per 5 mL

INJECTION
Pepcid® IV
(Famotidine|MSD)
20 mg per 2 mL

Contraindications: Hypersensitivity to any component.

Precautions: ***General:*** Symptomatic response to therapy does not preclude the presence of gastric malignancy.

Patients with Severe Renal Insufficiency: Longer intervals between doses or lower doses may be needed in patients with severe renal insufficiency (creatinine clearance <10 mL/min) to adjust for the longer elimination half-life of famotidine (see Clinical Pharmacology and Dosage and Administration sections of Prescribing Information).

Information for Patients: The oral suspension should be shaken vigorously for 5-10 seconds prior to each use, and unused constituted oral suspension should be discarded after 30 days.

Drug Interactions: No drug interactions have been identified. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine, and antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In rats and mice given oral doses up to approximately 2500 times the recommended human dose for active duodenal ulcer, there was no evidence of carcinogenic potential, no evidence of a mutagenic effect, and fertility and reproductive performance were not affected.

Pregnancy: *Pregnancy Category B*—There are no adequate or well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether famotidine is secreted into human milk; however, it is secreted into the milk of lactating rats. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: No dosage adjustment is required based on age but may be necessary in severe renal impairment (see Clinical Pharmacology section of Prescribing Information).

Adverse Reactions: The adverse reactions listed below have been reported during domestic and international clinical trials in approximately 2500 patients. In the placebo-controlled clinical trials, the incidence of adverse experiences with PEPCID Tablets, 40 mg at bedtime, was similar to that with placebo.

Incidence Greater than 1%: The following adverse reactions have been reported to occur in more than 1% of patients on therapy with PEPCID in controlled clinical trials and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%), and diarrhea (1.7%).

Causal Relationship Unknown: The following other adverse reactions have been reported in clinical trials. While a causal relationship could not be established for these infrequently reported events, causality cannot be excluded. *Body as a Whole*—Fever, asthenia, fatigue. *Cardiovascular*—Palpitations. *Gastrointestinal*—Nausea, vomiting, abdominal discomfort, anorexia, dry mouth, liver enzyme abnormalities. *Hematologic*—Thrombocytopenia. *Hypersensitivity*—Orbital edema, conjunctival injection. *Musculoskeletal*—Musculoskeletal pain, arthralgia. *Nervous System/Psychiatric*—Paresthesias; grand mal seizures (single report); psychic disturbances including depression, anxiety, decreased libido, hallucinations (single report); insomnia; somnolence. *Respiratory*—Bronchospasm. *Skin*—Alopecia, acne, pruritus, rash, dry skin, flushing. *Special Senses*—Tinnitus, taste disorder.

The adverse reactions reported for PEPCID Tablets may also occur with PEPCID Oral Suspension or PEPCID I.V.; in addition, transient irritation at the injection site has been observed with PEPCID I.V.

Management of Overdosage: There is no experience to date with deliberate overdosage. Up to 640 mg/day have been given to patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

Dosage and Administration: ***Duodenal Ulcer:*** The recommended adult oral dosage for active duodenal ulcer is 40 mg h.s.; most patients heal within 4 weeks, and it is rarely necessary to use the full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective. For maintenance therapy, the recommended oral dosage is 20 mg h.s.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas): The dosage varies with the individual patient; the recommended adult oral starting dosage is 20 mg q6h, but some patients may require a higher starting dosage. Dosages should be adjusted to individual patient needs and continued as long as clinically indicated; up to 160 mg q6h have been administered to some patients with severe Zollinger-Ellison syndrome.

Oral Suspension: The Oral Suspension may be substituted for Tablets for those patients who cannot swallow tablets.

Directions for Preparing PEPCID Oral Suspension: Prepare suspension at time of dispensing. Slowly add 46 mL Purified Water. Shake vigorously for 5-10 seconds immediately after adding the water and immediately before use.

Stability of PEPCID Oral Suspension: Unused constituted oral suspension should be discarded after 30 days.

Intravenous Administration: In some hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or in patients who are unable to take oral medication, the recommended intravenous dosage is 20 mg q12h. For preparation of solutions for injection or infusion and for compatible diluents, please see Prescribing Information. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Concomitant Use of Antacids: Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Severe Renal Insufficiency: In patients with severe renal insufficiency (creatinine clearance less than 10 mL/min), the elimination half-life of famotidine may exceed 20 hours, reaching approximately 24 hours in anuric patients. Although no relationship of adverse effects to high plasma levels has been established, to avoid excess accumulation of the drug, the dosage may be reduced to 20 mg h.s. or the dosing interval may be prolonged to 36 to 48 hours as indicated by the patient's clinical response.

How Supplied: Tablets, containing 20 mg or 40 mg famotidine, with hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide as inactive ingredients, in bottles of 30 and unit-dose packages of 100; Oral Suspension, containing per 5 mL after constitution with 46 mL Purified Water, 40 mg famotidine, with citric acid, flavors, microcrystalline cellulose and carboxymethylcellulose sodium, sucrose, and xanthan gum as inactive ingredients, and sodium benzoate 0.1%, sodium methylparaben 0.1%, and sodium propylparaben 0.02% added as preservatives, in bottles of 400 mg famotidine for constitution; Solution for intravenous injection, containing 10 mg famotidine per mL, with L-aspartic acid 4 mg, mannitol 20 mg, and water for injection q.s. 1 mL as inactive ingredients, and benzyl alcohol 0.9% added as preservative to the multidose vial, as 10x2-mL single-dose vials and as 4-mL vials.

For more detailed information, consult your MSD Representative or see Prescribing Information.
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Charity Hospital Experience with Long-term Survival and Prognostic Factors in Patients with Breast Cancer with Localized or Regional Disease

CARL M. SUTHERLAND, M.D.* and FRANCES J. MATHER, PH.D.†

Long-term survival, the prognostic effects of race, age, tumor size, number of positive nodes, and presence of grave signs (fixation, peau d'orange/edema, dimpling/retraction, satellite nodules, and ulceration) in this distribution of estrogen receptors (ERs) and progesterone receptors (PRs) were studied in 2480 patients (1815 blacks, 665 whites) diagnosed with localized or regional breast cancer at Charity Hospital of Louisiana at New Orleans (CHNO) from 1948 to 1985 and followed up in the CHNO Tumor Registry. Breast cancer-specific survival rates were 57%, 45%, 41%, 39%, 38%, and 35% at 5, 10, 15, 20, 25, and 30 years, respectively. Size of tumor, clinical status of nodes, and degree of fixation were important prognostic clinical factors; and number of nodes was an important pathologic factor with no additional value of the "grave signs." Size and fixation were related. Independent of size, clinical and pathologic status and fixation were related. ER was related to age and PR was related to number of nodes. The excess mortality from breast cancer at later intervals from diagnoses was small compared with mortality from other causes. Some, but not all, clinical findings were important prognostic indicators. ER and PR were related to some variables with unclear meaning.

ALMOST ALL LONG-TERM SURVIVAL STUDIES following a diagnosis of breast cancer have shown early high mortality from breast cancer and some increased mortality from breast cancer at late intervals. The overall magnitude of mortality, however, has varied considerably among studies.[1-8] In addition, various interpretations regarding "cure" of the disease and its systemic implications have been given.

Pathologic lymph node and estrogen receptor (ER) and progesterone receptor (PR) status are important as prognostic factors for survival in patients with breast cancer.[9] ERs and PRs are important markers for hormonal responsiveness of tumor, they appear to affect overall prognosis, and have been reported to vary in presence and concentration by patient and tumor characteristics, particularly by race.[10] The variations by race are not completely understood. Age, race, year of diagnosis, size of tumor, clinical node status, and grave signs have not been identified consistently as prognostic factors in patients with breast cancer.[1-7,9,11-22] Recent studies are frequently on patients entered in clinical trials and are restricted to the stage of disease and characteristics of patients enrolled in that trial.[7,11] Few univariate or multivariable analyses of the prognostic contributions of these factors have been performed in patients more representative of the total population with breast cancer. That restriction and its results on multivariable analysis in breast cancer have seldom been discussed. Also, few, if any, recent studies on comparison of clinical characteristics alone, particularly in regard to the "grave signs" *versus* clinical characteristics plus pathologic number of nodes over several stages, have been performed.

The Charity Hospital of Louisiana at New Orleans Tumor Registry (CHNO-TR) has entered and collected follow-up information on patients with cancer since 1947. The patients in this study are those with regional (skin, chest wall, or muscle attachment and no evidence of distant metastases in accordance with Surveillance, Epidemiology, and End Results [SEER] definition) and localized (no evidence of complete or incomplete skin, muscle, or chest wall attachment in accordance with SEER definition) disease. This population of patients

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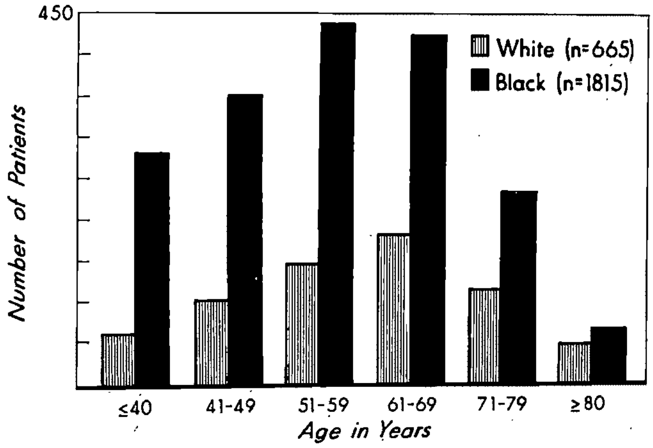

FIG. 1. Distribution of patients by age and race; all patients since 1948 (N = 2480).

with breast cancer is interesting because of its size (2480), length of follow-up (nearly 40 years for some patients), uniformly lower socioeconomic status, large proportion of black patients, and large proportion of patients with locally advanced disease. This study attempted to determine in these patients: (1) effect of breast cancer on long-term survival; (2) prognostic effect of age, race, year of diagnosis, size of tumor, clinical node status, presence of certain grave signs, and pathologic node status; (3) comparison of the prognostic effect of clinical findings alone to that of clinical findings combined with pathologic node status; and (4) the relationship of ER and PR status to other clinical and pathologic variables.

Patients and Methods

Inclusion Criteria

Included in this study were 2480 patients (1815 blacks, 665 whites), who met the following criteria: (1) enrollment and follow-up in the CHNO-TR between January 1, 1948 and December 31, 1981, from all services of Tulane University School of Medicine (T), Louisiana State University School of Medicine (L), and an Independent Service (no longer active) (I), follow-up information on I and T patients only, 1982 through 1985, and new patient entry on T patients only from 1982 through 1985; (2) diagnosis made at CHNO of malignant breast cancer without evidence of distant metastases, including positive supraclavicular nodes excluded from this study at first diagnosis; (3) either a single breast primary or the first of two or more breast primaries; (4) female of known race; (5) sufficient information available on diagnosis to establish stage of disease; (6) diagnosis was not an incidental finding at autopsy; and (7) no previous diagnosis of cancer. Of the 3443 potential tumors, 963 were excluded from analysis: 611 because the initial diagnosis was not made at CHNO, 197 because the tumor was not the only primary or the first of two or more primaries, eight because the tumor was not considered malignant by CHNO standards, three because the race was unknown, 118 because the patients were diagnosed from 1982 through 1985 and had an L number, 24 because the sex was male or unknown, and two because they did not have sufficient information for diagnosis of stage.

Age and Race Distribution

Figure 1 shows that the majority of patients in all age groups were black. The distribution by race was fairly similar at all ages, except in the older age categories where some decline was noted in the ratio of blacks to whites, probably reflecting the referral patterns of patients to CHNO.

Pathology

All patients with a diagnosis of invasive carcinoma were included. Those with other cancers of the breast, including sarcoma and noninvasive carcinoma, were excluded.

Type of Primary Therapy

The primary course of treatment in these patients was surgery only (43%); surgery and radiation (31%); surgery and chemotherapy (11%); radiation only (4%); and other treatments, including chemotherapy, hormonal treatment, and no surgery or radiation (11%). In all, 9% of the patients did not have surgery.

Classification by Cause of Death

All deaths were classified by the CHNO-TR according to status at death as follows: (1) no evidence of primary cancer (32%); (2) no evidence of primary cancer, but another cancer present (3%); (3) primary cancer present (62%); and (4) cancer status unknown (3%).

Lost to Follow-up

Of the patients not known to be dead, who were diagnosed during 1948 through 1985, 85% were contacted within the last 2 years; of those diagnosed during 1968 through 1985, 95% were contacted within the last 2 years.

Statistical Analysis

Survival curves were computed by means of actuarial methods in the BMDP series of computer programs (BMDP1L).[23] Breast cancer-specific curves were obtained by treating deaths resulting from causes other than breast cancer (CHNO-TR definition: no evidence of primary cancer or no evidence of primary, but another cancer present or cancer status unknown) as censored. Significant differences between survival curves were tested, using the generalized Savage (Mantel-Cox) test.[23] Cox's regression model[24] was used to evaluate the contribution of prognostic factors (BMDP2L).[23] Hazard rates for deaths from other causes were obtained from actuarial life tables (BMDP1L),[23] with deaths from breast cancer treated as censored.

Expected deaths were computed by adding the contributions of female age-, race-, year-, and breast cancer-specific death rates for the Louisiana population applied to individual follow-up times. These rates were obtained from Louisiana decennial population counts and deaths reported by the Department of Vital Statistics of the United States and the Louisiana Department of Health and Human Resources—Vital Statistics. The expected deaths were expressed as a proportion of this study population to provide an expected death rate for comparison.

The effect of prognostic variables in the multivariate Cox analysis was evaluated by means of the log likelihood test; *i.e.*, the quantity 2(LL[full model, df = kl] − LL [partial model, df = k2]) is distributed as chi-square with k1–k2 degrees of freedom.[25]

Degree of fixation was represented by two dummy variables (T_1 and T_2), both coded (0, 0) to represent the background group of no-fixation, incomplete (0, 1), and complete (1, 0). The relationship among degree of fixation, tumor size, clinical status, and number of nodes was investigated by means of log linear modelling (BMDP4F).[23,26] The relationship between the square root of ER and PR status and other prognostic variables was investigated by means of linear regression (BMDP2R).[23,27] The square root of ER and PR was used as a normalizing transformation on the skewed distribution of these variables.

Results

Breast Cancer-Specific Survival

Survivorship of all patients (combined localized and regional diseases, N = 2452), with other causes of death removed, illustrated the initial high mortality caused by breast cancer in the first 5 years after diagnosis, declining in mortality in the second and third 5-year periods, and little mortality after 15 years. The breast cancer-specific survival rate was 57%, 45%, 41%, 39%, 38%, and 35% at 5, 10, 15, 20, 25, and 30 years, respectively (Fig. 2). The survivorship of patients classified with localized (N = 1167) or regional (N = 1285) disease is shown in Figure 3. The survival pattern was similar among patients with localized disease: 74%, 65%, 61%, 57%, 56%, and 53% at 5, 10, 15, 20, 25, and 30 years, respectively, and regional disease: 40%, 28%, 24%, 23%, 22%, and 20% at 5, 10, 15, 20, 25, and 30 years, respectively, although of more magnitude in regional disease.

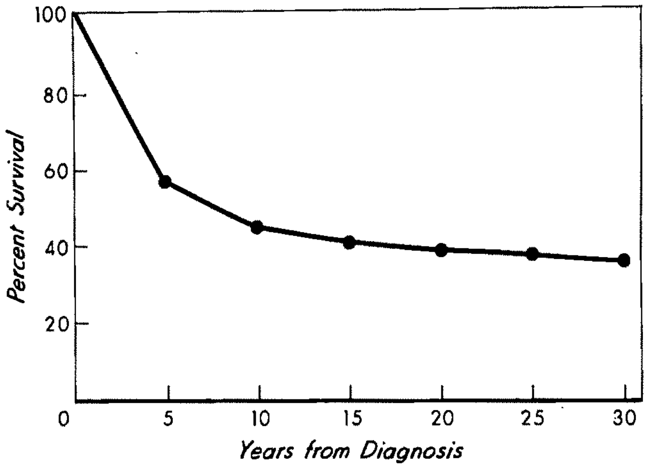

FIG. 2. Breast cancer-specific survival; all patients since 1948 (N = 2452).

After 1968, pathologic node status was recorded on a majority of patients. The effect of nodal status among patients with localized disease compared with regional disease is shown in Figure 4. The 5-, 10-, and 15-year survival rates of patients with localized node-negative disease (N = 275) were 85%, 75%, and 66%, respectively; with localized node-positive disease (N = 168), 59%, 44%, and 37%, respectively; and with regional disease (N = 379), 46%, 33%, and 29%, respectively.

The improved survival from breast cancer given survival to 5 years is shown in Figure 5. The survival rate from breast cancer only to 10 and 15 years, conditional on survival to 5 years, was 88% and 78% among node-

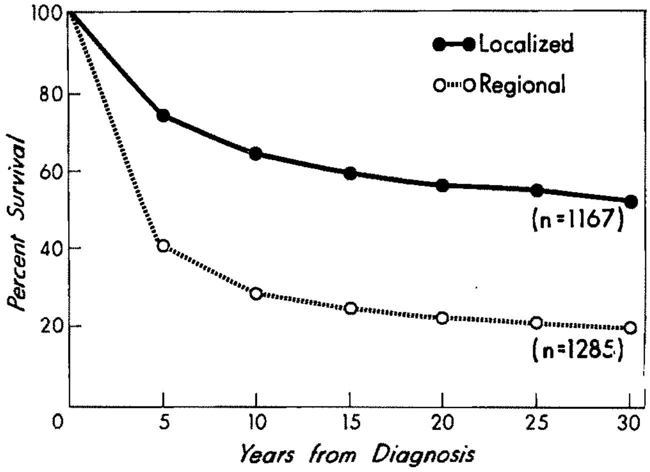

FIG. 3. Breast cancer-specific survival; all patients since 1948 by stage (N = 2452).

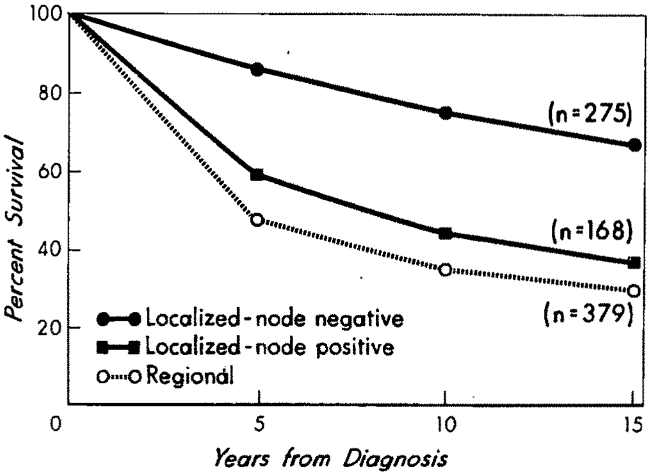

FIG. 4. Breast cancer-specific survival; all patients since 1968 by stage (N = 822).

negative patients with localized disease, 75% and 63% among node-positive patients with localized disease, and 72% and 63% among those with regional disease.

Annual Hazard Rates

In calculating the annual breast cancer-specific hazard rates, initial high mortality rates were found in the first 5 years, decreasing to lower levels over time. The effect of competing risks or other causes of death in this population varied with age. Among patients over 65 years of age, the risk of death from other causes exceeded that from regional breast cancer by 10 years from diagnosis, and from localized breast cancer by 5 years from diagnosis. Among patients 50–65 years of age, the risk of death from other causes exceeded that from regional disease by 12–15 years, and from localized disease by 10 years from diagnosis. In patients less than 50 years of age, the risk of death from other causes did not exceed the risk from regional breast cancer from 17 to 20 years from diagnosis, and in localized breast cancer from 10 to 15 years. The risk of death from breast cancer in this population always exceeded that in the general population of comparable age and race (Fig. 6).

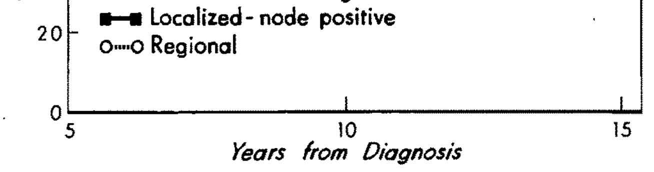

FIG. 5. Breast cancer-specific survival given survival to 5 years; all patients since 1948 by stage (N = 356).

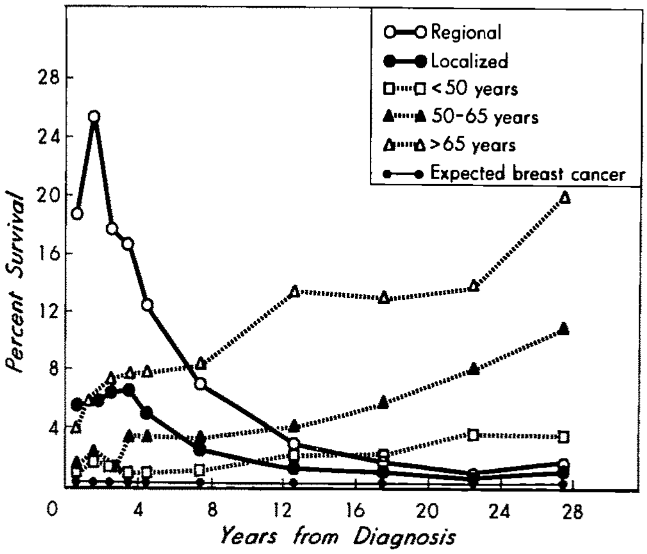

FIG. 6. Annual breast cancer-specific hazard rate by stage and other cause hazard rate by age; all patients since 1948 and the expected breast cancer-specific general population hazard rate (N = 2452).

Univariate Assessment of Prognostic Factors

The effects of several variables believed to be of prognostic significance were evaluated in a univariate analysis by means of the Cox proportional hazard model. Number of positive nodes, increasing size of tumor, degree of fixation (complete > incomplete > none), presence of ulceration, edema, peau d'orange, dimpling/retraction, positive clinical status of nodes, and earlier year of diagnosis were all associated with increased hazard of death caused by breast cancer. Only age at diagnosis, presence of satellite nodules, and race were not associated with the hazard caused by breast cancer (Table 1).

TABLE 1. *Univariate Assessment of Prognostic Factors*

Clinical Variables	p Value
Number of positive nodes (0–38)	0.00
Size of tumor (<1 cm to 8 cm or more)	0.00
Fixation (none, incomplete, complete)	0.00
Ulceration (present, absent)	0.00
Edema (present, absent)	0.00
Peau d'Orange (present, absent)	0.00
Dimpling/retraction (present, absent)	0.00
Clinical status of nodes (negative, positive)	0.00
Year of diagnosis (68, 69 . . . 85)	0.04
Age at diagnosis (21 . . . 94)	0.71
Satellite nodules (present, absent)	0.74
Race (black, white)	0.84

Multivariate Assessment of Prognostic Factors

Evaluation of Prognostic Significance of Clinical Signs. The effect of clinical factors—size of tumor, clinical status of nodes, and degree of fixation (complete *vs.* none and incomplete *vs.* none)—in comparison to several controlling factors also included in the model (race, age, and year of diagnosis) were evaluated in a multivariate model. Increasing size of tumor, positive clinical status of nodes, and degree of fixation (complete and incomplete) were all significantly related to increasing hazard of death caused by breast cancer. Neither age at diagnosis, race, nor year of diagnosis was significantly associated with the hazard of death resulting from breast cancer in this population (Table 2). A further analysis attempted to assess the importance of any interactions between the clinical variables: (1) size and clinical status, (2) clinical status and fixation, or (3) size and fixation. Neither of the first two interactions contributed significantly to the hazard. When the third term (size by fixation) was included in the analysis, however, the interaction was nearly colinear (closely related) with terms already in the model. Thus, it was impossible to evaluate the joint effect of these variables on survival.

The effect of clinical status of nodes and degree of fixation on survival is seen in the 5-year survival rates in Table 3. The mean size of tumor was similar between negative and positive clinical status within a fixation group. The mean size of tumor did, however, increase with degree of fixation (Table 4).

Evaluation of Prognostic Significance of Grave Signs. Effects of grave signs, ulceration, peau d'orange, satellite nodules, dimpling/retraction, and edema were evaluated by comparing two models: one containing grave signs and the current model variables such as age at diagnosis, race, year of diagnosis, size of tumor, clinical status of nodes, and degree of fixation (complete fixation *vs.* none and incomplete fixation *vs.* none) to control for known clinical prognostic factors *versus* the current model containing only the clinical prognostic factors. No significant effect of any grave signs was detected after controlling for known clinical factors (chi-square = 2 (−1631 − [−1634]) = 6, 5 df, $p > 0.3$).

TABLE 2. *Cox Proportional Hazard Analysis of Clinical Prognostic Factors*

Variable	Coefficient	Standard Error	Coefficient/ Standard Error	Relative Risk
Race	−0.069	0.178	−0.4	0.93
Age at diagnosis	−0.009	0.005	−1.8	0.99
Year of diagnosis	−0.018	0.017	−1.0	0.98
Size of tumor	0.103	0.030	3.4*	1.11
Clinical status	0.767	0.135	5.7*	2.15
Complete fixation (T_1)	0.662	0.173	3.8*	1.94
Incomplete fixation (T_2)	0.458	0.166	2.8*	1.58

* Significant $p < 0.01$.

Coding: race (0-white, 1-black); age at diagnosis in years (21 . . . 94); year of diagnosis in years (68 . . . 85); size of tumor (1 . . . 8, 9 cm or more); clinical status (0-negative, 1-positive); complete fixation (0-no, 1-yes); incomplete fixation (0-no, 1-yes).

Evaluation of Prognostic Significance of Pathologic Node Status in Addition to Clinical Signs. The effect of pathologic node status was evaluated by adding it to the current model containing the clinical signs and age at diagnosis, race, and year of diagnosis. The number of positive nodes was significantly associated with increasing hazard. Further, in an analysis of interaction terms, only fixation by pathologic node status was included, suggesting that the effect of number of positive nodes and degree of fixation on the hazard resulting from breast cancer were slightly less among those with incomplete and complete fixation compared with the no-fixation group (Table 5).

The decreasing survival with number of positive nodes, degree of fixation, and clinical status of nodes is illustrated by 5-year survival rates in Table 6. Association of size with fixation is shown, as is the lack of relation between size and number of nodes and clinical status (Table 7).

Relationship Between Size, Pathologic Nodes, Clinical Status, and Fixation

Some relationship was expected among size of tumor, nodes, clinical status, and degree of fixation. Degree of

TABLE 3. *Five-year Survival Rates ± Standard Error in Clinical Model*

	Fixation					
	None		Incomplete		Complete	
Clinical Status	Survival Rates	No. of Patients	Survival Rates	No. of Patients	Survival Rates	No. of Patients
Negative	0.78 ± 0.02	371	0.73 ± 0.06	63	0.51 ± 0.06	73
Positive	0.55 ± 0.05	110	0.40 ± 0.06	70	0.28 ± 0.05	76

TABLE 4. *Mean Size of Tumors ± Standard Error in Clinical Model*

	Fixation					
	None		Incomplete		Complete	
Clinical Status	Mean Size of Tumors	No. of Patients	Mean Size of Tumors	No. of Patients	Mean Size of Tumors	No. of Patients
Negative	3.9 ± 0.1	340	4.9 ± 0.3	59	5.9 ± 0.3	64
Positive	4.4 ± 0.2	100	4.7 ± 0.3	66	6.6 ± 0.3	60

fixation was related to size of tumor (no fixation with smaller tumors, incomplete fixation with larger tumors, and complete fixation with the largest tumors) (Fig. 7). Clinical status had no effect on size of tumor beyond degree of fixation (possibly a trend in the complete fixation group) (Fig. 8), nor did the nodal status have any effect (Fig. 9) except slightly in the group with no fixation (Fig. 10).

Independent of size, however, a complicated relationship existed between the number of positive nodes, degree of fixation, and clinical status. An increased number of positive nodes was observed for clinically positive patients relative to clinically negative patients among those with incomplete or no fixation. In the group with complete fixation, however, little difference was observed between those with clinically positive or negative nodes with respect to number of positive nodes (Fig. 11).

Estrogen Receptor (ER) and Progesterone Receptor (PR) Status Relationship to Other Variables

The ER (N = 54) status and PR (N = 52) status have been collected since 1981. The relationship between these hormonal variables and race, age, number of positive nodes, clinical status, size, and fixation was investigated (Table 8). ER status increased with age ($p < 0.001$) and lower ER with clinically positive node status was observed ($p < 0.025$). No evidence existed that race, number of positive nodes, size, or degree of fixation was related to ER. In a multivariate evaluation, ER increased with age ($p < 0.001$); however, the relationship between ER and clinical status of nodes was of borderline importance ($0.05 < p < 0.10$). Tumor size, race, number of positive nodes, and degree of fixation were not related to ER status (Table 9). The relationship between PR status and prognostic variables was examined by univariate methods (Table 10). PR was found to increase with number of nodes ($p < 0.05$). No relationship was observed between PR and race, age, size of tumor, clinical status, and degree of fixation. In a multivariate analysis, the same findings were observed (Table 11).

Discussion

Long-term Survival

An excess of deaths from breast cancer was found in this study at all time intervals: large at early follow-up times, declining at later follow-up times. This finding is similar to that documented in most other long-term studies; *e.g.*, the hazard rate in the first 5 years from death caused by breast cancer in this study was similar to that from all causes reported by Langlands et al.[1] At later time intervals, however, comparison was not appropriate because of the difference in definition of hazard.

TABLE 5. *Cox Proportional Hazard Analysis of Clinical and Pathologic Node Prognostic Factors*

Variable	Coefficient	Standard Error	Coefficient/ Standard Error	Relative Risk
Race	−0.088	0.178	−0.5	0.92
Age at diagnosis	−0.006	0.005	−1.1	0.99
Year of diagnosis	−0.025	0.018	−1.4	0.98
Size of tumor	0.107	0.031	3.5*	1.11
Clinical status	0.474	0.144	3.3*	1.61
Complete fixation (T_1)	0.958	0.200	4.8*	2.61
Incomplete fixation (T_2)	0.499	0.208	2.4*	1.65
Pathologic nodes	0.101	0.016	6.3*	1.11
Pathologic nodes × complete fixation†	−0.079	0.028	−2.8*	0.92
Pathologic nodes × incomplete fixation†	−0.037	0.023	−1.6*	0.96

* Significant $p < 0.01$.

† These interaction terms are computed as the product (×) of pathologic nodes and each of the two fixation variables, T_1 and T_2.

Coding: Race (0-white, 1-black); age at diagnosis in years (21 . . . 94); year of diagnosis in years (68 . . . 85); size of tumor (1 . . . 8, 9 cm or more); clinical status (0-negative, 1-positive); complete fixation (0-no, 1-yes); incomplete fixation (0-no, 1-yes); pathologic nodes (0 . . . 38).

TABLE 6. *Five-year Survival Rates ± Standard Error (N) in Clinical and Pathologic Node Model*

		Fixation					
		None		Incomplete		Complete	
Clinical Status	Nodes	Survival Rates	No. of Patients	Survival Rates	No. of Patients	Survival Rates	No. of Patients
Negative	0	0.86 ± 0.02	239	0.85 ± 0.06	34	0.51 ± 0.08	41
	1–3	0.86 ± 0.06	44	0.55 ± 0.14	15	0.57 ± 0.17	11
	4^+	0.48 ± 0.09	33	0.56 ± 0.17	10	0.47 ± 0.15	16
Positive	0	0.82 ± 0.08	24	0.53 ± 0.12	19	0.24 ± 0.07	38
	1–3	0.58 ± 0.09	32	0.72 ± 0.17	8	0.43 ± 0.14	13
	4^+	0.41 ± 0.08	41	0.32 ± 0.08	40	0.24 ± 0.10	21

As the hazard rate from breast cancer declined at later intervals, the hazard rate from other causes increased because other causes were primarily a function of the increasing age of the patient and, to some extent, race or socioeconomic status, and date of diagnosis, among other mortality risk factors.

Several studies[2,5,7] reported that 75–85% of all deaths that occurred in the breast cancer population studied were caused by breast cancer. Some may interpret this as the probability of eventual death resulting from breast cancer. Our study, restricted to regional and localized disease, reported 62% of all deaths with breast cancer. The probability of patients eventually dying of breast cancer remains a function of: (1) death caused by breast cancer, which depends on the prognostic factors at time of diagnosis such as stage of disease and number of nodes, and (2) deaths resulting from other causes, which depend on age, race and/or socioeconomic status, and date of diagnosis. The ratio of breast cancer deaths to total deaths is, thus, confounded by these factors and is not a measure of the probability of patients eventually dying of breast cancer. Estimation of the risk of eventual death from breast cancer should be computed by life-table methods, based on prognostic factors at diagnosis of breast cancer and other causes of death.

Several authors[1–6,8] have discussed the results of long-term studies in relation to "cure" and breast cancer as a systemic disease. The discussions are based on a population definition of cure to evaluate the efficacy of cancer treatment. The concept is attributed to Greenwood (cited in Lee,[28] who stated: "If an examination of the after histories of such patients showed that on the average they lived as long as a random sample of persons in the same age, sex, occupation, etc., nobody could object to the use of the word 'cure.' " (p. 96).

Almost all studies show an excess in breast cancer deaths over that expected in the general population. This excess of deaths may be interpreted by some as evidence, by the above definition, that the breast cancer population is not cured. The methodologic issues that may be responsible for the excess, such as distribution of other causes of death in the reference population and breast cancer population and difficulty in allocation of deaths by cause,[29] is discussed elsewhere. We believe there is little reason to interpret this excess mortality as an indication of incurability or presence of systemic disease in the total breast cancer population. Regardless of interpretation, the excess is small at late intervals, particularly in relation to deaths from other causes.

Prognostic Factors

In previous studies of prognostic factors in this patient population when patients where classified by clinical

TABLE 7. *Mean Size of Tumors in Clinical and Pathologic Node Model*

		Fixation					
		None		Incomplete		Complete	
Clinical Node Status	Pathologic Node Status	Mean Size of Tumors	No. of Patients	Mean Size of Tumors	No. of Patients	Mean Size of Tumors	No. of Patients
Negative	0	3.7 ± 0.1	218	5.2 ± 0.4	33	6.0 ± 0.4	37
	1–3	4.2 ± 0.3	41	3.8 ± 0.4	13	6.5 ± 0.7	10
	4^+	4.4 ± 0.3	31	5.0 ± 0.5	10	5.2 ± 0.6	14
Positive	0	3.8 ± 0.5	22	5.1 ± 0.5	18	7.5 ± 0.3	28
	1–3	4.7 ± 0.6	29	4.9 ± 0.6	8	4.9 ± 0.5	12
	4^+	4.4 ± 0.3	37	4.5 ± 0.3	37	6.4 ± 0.6	17

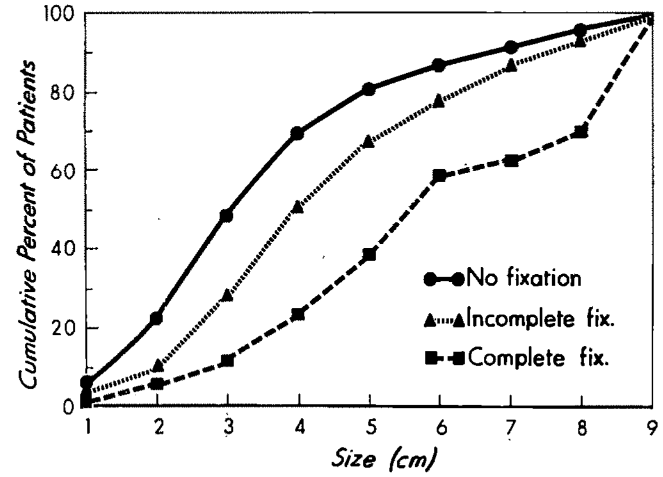

FIG. 7. Tumor size by degree of fixation without regard for pathologic or clinical node status (N = 615).

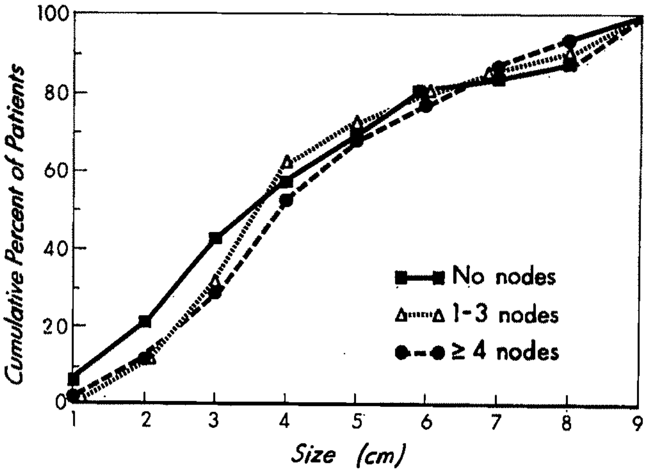

FIG. 9. Tumor size by pathologic node status without regard for degree of fixation or clinical status (N = 615).

stage into regional[30] and localized[29] disease, a weak relationship was found between size and prognosis, a finding in general agreement with other studies with similar patient populations.[11,15,17,19-22] This study found an overall effect of tumor size on breast cancer-specific survival. In addition, a relationship of size to fixation was found. These findings may be explained as follows: when the patient populations are restricted by stage or other characteristics, prognostic factors also restricted by this classification may not appear as significant.

The relationship of increasing number of nodes to decreasing survival and increasing percentage of pathologically positive nodes with clinically positive status has been well documented. In this study, we found an independent additional effect of clinical status on survival (decreasing survival with clinically positive status) after controlling for number of pathologically positive nodes.

The relationship between size, fixation, clinical status, and number of nodes needs clarification. Clinical observation and some studies have found increased size was related to increased number of nodes[17] and, one would expect, with being clinically positive. When fixation was not controlled, this relationship was found. When the population was classified by fixation, no clinically significant relationship between size and pathologic nodes or size and clinical status was observed. Within each fixation group, the distribution of tumor size was independent of number of nodes and clinical status; however, because tumor size was related to degree of fixation, a correlation between tumor size and clinical status or pathologic nodes was found when fixation was not controlled.

The lack of prognostic importance of the traditional grave signs is in accordance with some other studies.[19-22]

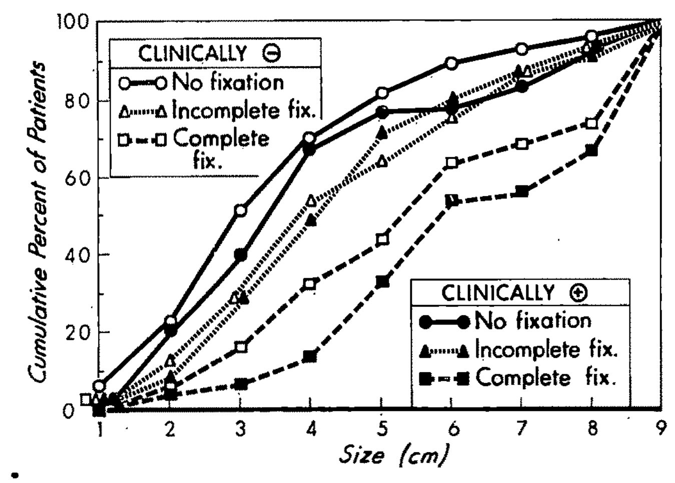

FIG. 8. Tumor size by clinical status and degree of fixation without regard for pathologic node status (N = 615).

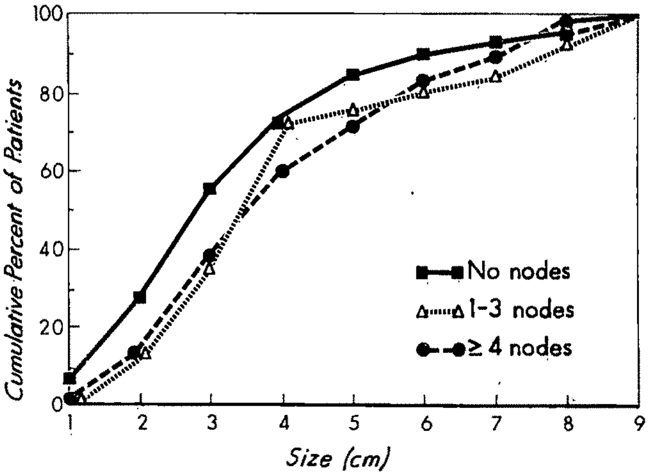

FIG. 10. Tumor size by number of pathologic nodes in patients with no fixation without regard for clinical node status (N = 378).

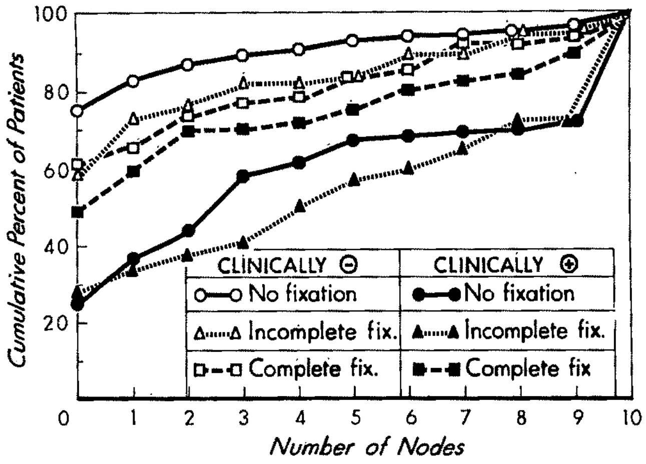

FIG. 11. Number of pathologic nodes by clinical status of nodes and fixation without regard for size (N = 615).

TABLE 9. *Multivariate Assessment of Estrogen Receptor and Prognostic Variables*

Prognostic Variables	p Value
Age	<0.001
Clinical status of nodes	$0.05 < p < 0.10$
Tumor size	>0.25
Race	>0.25
Number of positive nodes	>0.25
Degree of fixation	>0.25

The grave signs may be ignored when predicting survival if size, fixation, and clinical status are known.

Any study of prognostic factors is subject to the unknown bias caused by lead-time (the time from first possible diagnosis to actual diagnosis) differences. This patient population contains a significant number of women in whom tumors have been present for long periods. Multiple factors send women to health care facilities for a diagnosis. Some women refer themselves at the first possible finding of a small lump in the breast, whereas other breast cancers are found at admission to the hospital for other causes. Some patients are admitted when the symptoms of metastatic disease or localized problems are intolerable. The bias of varying lead times on the identification of prognostic variables in cancer is unknown, but probably affects findings.

The complete axillary node dissection is not without its complications. How important is an axillary node dissection for prognostic information in care of the patient population? With current interest in perioperative adjuvant therapy, clinical trials may be developed in the near future in which therapy other than surgery may be delivered first and, thus, axillary lymph node status will be unknown. How well can prediction of survival be made on the basis of clinical factors alone? We studied the additional contribution of pathologic node status as a prognostic factor beyond clinical factors alone and found in patients with incomplete or no-fixation that prognosis depends on pathologic node involvement. Among those with complete fixation, survival depends on clinical status of nodes. Whether an axillary dissection should be performed for prognostic information depends on: (1) if a variation exists in prognosis by axillary node status, and if it does, whether this knowledge can be used to select a treatment that will improve survival; and (2) if the proportion of patients misclassified can be justified. As one gets to larger tumors with increased fixation, the differences in breast cancer-specific survival are far less by axillary node status, and dissection of the axilla may not be necessary for prognostic information. In the best prognostic group of patients (66) with tumors less than 2 cm, no fixation, and clinically negative axilla, a 12% (8/66) rate of pathologically positive nodes was found. Whether an axillary node dissection is necessary to find the 12% of patients is a function of the above criteria.

As in our previous studies[29,30] we found no relationship of age and race to survival. This finding of no difference by age and race is at variance with some other studies and popular clinical belief.[7,12-16] Our previous studies found no relationship of race to survival in this fairly uniform low-socioeconomic group of black and white patients and noted that another study[31] found no differences in survival by race when socioeconomic status was controlled, suggesting that differences in survival by race were due primarily to differences in socioeconomic status rather than race.

Estrogen Receptor (ER) and Progesterone Receptor (PR) Relationships

Because ER and PR values have been collected only since 1981, the follow-up time on the patients is too

TABLE 8. *Univariate Assessment of Estrogen Receptor and Prognostic Variables*

Prognostic Variables	p Value
Age	<0.001
Clinical status of nodes	<0.025
Tumor size	>0.25
Race	>0.25
Number of positive nodes	>0.25
Degree of fixation	>0.25

TABLE 10. *Univariate Assessment of Progesterone Receptor and Prognostic Variables*

Prognostic Variables	p Value
Number of nodes	<0.05
Fixation	$0.10 < p < 0.25$
Age	>0.25
Clinical status	>0.25
Tumor size	>0.25
Race	>0.25

TABLE 11. *Multivariate Assessment of Progesterone Receptor and Prognostic Variables*

Prognostic Variables	p Value
Number of nodes	<0.05
Age	>0.25
Fixation	>0.25
Tumor size	>0.25
Clinical status	>0.25
Race	>0.25

short to make any statement regarding the relationship of ER and PR to survival. Our findings of no relationship of ER to size and number of nodes, and increasing proportion of ER and increasing concentration of ER with increasing age, are in general agreement with other studies.[10] Our finding of no relationship with race is consistent with some and not with others,[10] but is consistent with our previous findings of no differences in any variable studied by race in this breast cancer population.

Our finding of a possible relationship between ER and clinical node status, to our knowledge, has not been confirmed by other studies. That decreasing ER may be related to positive clinical node status and positive clinical node status is related to decreased survival is in keeping with the idea that negative ER is related to tumor differentiation with decreased differentiation related to decreased survival.

Of interest is the increasing ER with increasing age, but no relationship of increasing age to survival. This finding suggests that properties of ER are related to age separate from their relationship to survival.

The relationship between PRs and other patient and tumor characteristics has not been reported as extensively as that of ERs. This study found no relationship between PRs and any factors other than increasing number of pathologic nodes. These data seem unusual, in that an increasing PR level was found to be related to increased survival by Clark et al.[9]; however, it is also of interest that Clark's study found survival was decreased in those patients for whom PR information was known over those not known. Fisher et al.[32] reported no relationship of PR to number of nodes in a group of axillary node-positive patients with a different type of analysis, and Fisher et al.[33] reported a weak relationship of PR+ to 1 to 3 nodal metastases as opposed to 4+ in a subset of the same patients. The relationship between our findings, those of the above authors,[9,32,33] and the overall distribution and significance of PRs remains unclear.

Some care should be taken in interpreting the relationship of ER and PR because of the selection process in obtaining these values. Tumors too small to be assayed are not included; thus, the relationship of other variables to ER and PR are conditional on this selection process.

Acknowledgments

The authors thank Charity Hospital of Louisiana at New Orleans (CHNO), the CHNO Tumor Registry, the Department of Surgery of Louisiana State University School of Medicine, and all CHNO faculty, staff, and house staff involved in the care of these patients, Gae O. Decker-Garrad for manuscript preparation, and Winifred Hunter for typing.

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DISCUSSION

DR. EDWARD M. COPELAND III (Gainesville, Florida): Dr. Sutherland asked me if I would discuss this paper, and I am very happy to do so.

Kirby Bland and I were asked to review the papers on breast diseases presented at the Southern Surgical Association meetings for the last 100 years. I will have the pleasure of presenting this material to you later in the program, but there are some slides that I will not be able to include in that report. I thought you might now enjoy seeing those that deal with prognostic indicators for breast cancer.

(Slide) This slide is from a paper given by Burton J. Lee of New York in 1932. It shows that regardless of which quadrant of the breast the cancer arose from, the three-year survival rate was the same. Lee also gets credit for having pointed out that axillary metastasis is the most important prognostic indicator for breast cancer.

(Slide) In 1956, Drs. Alrich, Liddle, and Morton of Charlottesville also evaluated the quadrant in which the cancer arose as a prognostic variable and found the percentage of patients with axillary metastasis and the five-year survival to be the same regardless of the quadrant of origin.

(Slide) This slide is from a paper by Nicolson and Grady given in 1947. The patients were from the Steiner Breast Clinic in Atlanta. The data shown indicate that as the size of the breast cancer increases in diameter, the five-year survival rate decreases. Thus, in 1947 (actually even before that time), the size of the lesion was recognized as a major prognostic indicator.

(Slide) Stewart Harrington gave several presentations before the Southern Surgical Association between 1946 and 1952. He reviewed the radical mastectomy data from the Mayo Clinic. This slide is of 8,563 patients followed for up to 30–45 years. Positive lymph nodes occurred in 63.7% of the patients, whereas 36.3% had negative nodes. All deaths were assumed to be from malignant disease, and even at the 30–45 year interval, 14% of the patients with negative nodes were still alive. This data from 1952 questions whether or not breast cancer is always a systemic disease since lengthy survival was obtained with surgery as the only modality of therapy.

(Slide) In 1961, associated pregnancy as a prognostic variable was evaluated by Byrd and Stevenson of Nashville. Overall, five-year survival was 55.2% for 29 patients. Patients with positive nodes had a 28% five-year survival, whereas 11 patients with negative nodes had a 100% five-year survival. This data showed that pregnancy *per se,* when associated with negative axillary lymph nodes, was not a poor prognostic indicator.

(Slide) In 1960, similar data on pregnancy was demonstrated by Horsley and Alrich of Charlottesville. All patients with negative nodes and associated pregnancy survived for the five-year interval.

I would like to ask Dr. Sutherland about two therapeutic points, since he has reviewed a large number of patients from Charity Hospital treated over a lengthy period of time. Did either radiation therapy or the type of surgical procedure done affect long-term survival?

DR. LOREN J. HUMPHREY (Shawnee Mission, Kansas): I wish to thank Dr. Sutherland for affording me the opportunity of reviewing this manuscript.

This paper brings forth new data and some invaluable contributions as an extension of initial studies reported previously from the Charity Hospital, New Orleans Tumor Registry, and, indeed, by Dr. Sutherland himself.

Allow me to initiate my comments, if you will, by making an observation that, while seeming tumidic, might otherwise be lost in this sea of data, which you will notice when you read the manuscript.

The data—culled by several surgeons (and at least two teaching services) from the tumor registry comprising patients' results—stands as a witness to the great value of that instrument called the tumor registry. For those of us who have worked for many years in the Cancer Commission of the American College of Surgeons, and for the college, insisting on the exigency for maintaining a tumor registry in cancer program approvals, this paper is a reward for our perseverance. The large number of patients with excellent long-term follow-up data only as seen in tumor registry data is the backbone of this paper. The plethora of data and its univariate and multivariate analysis is a real contribution. These data and their analyses should strike the death knell for some all-too-popular misconceptions. Indeed, when I study and ponder over this, I can only use one or two as an example.

First, Dr. Sutherland has shown that not all breast cancer patients die of breast cancer. Indeed, by 30 years, 36% of those were still surviving. "Therapeutic nihilism"—I wonder where it has gone when we realize that. I urge you to study this paper in detail and discern the many interrelationships of size, nodal status, and grave signs to prognosis.

I would highlight this by asking Dr. Sutherland: Considering the seeming independence of certain variables on survival, can you then attribute this effect to biologic behavior of certain tumors? For example, the survival of clinically negative patients with fixation is almost the same as clinically node positive patients without fixation.

Finally, prompted by the current trend toward conservative treatments of breast cancer and their attendant high local recurrence rate, I wonder: Will you be able to continue these studies by applying your multivariate analysis to risk of local recurrence, its subsequent treatment and the survival therefrom?

DR. ROBERT M. BEAZLEY (New Orleans, Louisiana): Thank you, Ted. In reviewing 2480 patients from the Charity Hospital in New Orleans tumor registry, the authors have reaffirmed the observation that tumor size and nodal status are key prognostic features of breast cancer. I think the "therapeutic nihilism" that this is not a curable disease has been fostered on us by our medical oncologist colleagues, and this information does to a large measure put that to rest.

It would have been of interest to evaluate some of the recently described prognostic factors such as cellular differentiation, tumor necrosis and tumor markers, particularly in the long-term survivors to see their predictive value.

I have one question for the authors, and that is, in your 1985 publication, using some of the same patients, you concluded that nodal status and peau d'orange were statistically the most important prognostic factors in long-term survival. In view of your presentation here, peau d'orange does not seem to carry the same precedence, and I wonder if you have any comments on that?

Finally, I would like to congratulate Dr. Sutherland on his election to membership and a well presented paper. However, I would be remiss if I failed to express my disappointment in his failure to heed our expressed wish that he not include the LSU patient data from the Charity Hospital Tumor Registry in his paper.

DR. JOHN D. PIGOTT, JR. (Memphis, Tennessee): Congratulations to Dr. Sutherland for affording us this information from a tremendous data base. Few private hospitals have so many good records for such a long period.

An element that has disturbed me for a long time and that affects many of our breast patients will be introduced into the long-term survival situation. That is, the effect of aggressive systemic therapy (chemotherapy) on long-term survival.

(Slide) This graph from Baptist Memorial Hospital, Memphis, shows ten years' survivals from date of treatment of 800 patients out of about 1900 treated from 1965–1973. Note that 28% of those who had positive axillary nodes were alive and well ten years later (prechemotherapy years).

(Slide) This slide, from 1974–1983, very nearly duplicates the previous one. The graph is based on only 238 patients who are eligible for ten years evaluation, about 27% of axillary node positive patients are alive without demonstrable cancer ten years after treatment (chemotherapy years).

If aggressive systemic therapy or adjuvant therapy for breast cancer is beneficial, then the group of patients with positive axillary nodes should reflect that benefit. There have been two reports that aggressive systemic therapy did not increase five-year survival. Our data indicates no difference in ten-year survival between the two groups.

My question: Did you consider or evaluate systemic therapy in your patients' survival data?

DR. MARSHALL URIST (Birmingham, Alabama): I would like to congratulate Dr. Sutherland on a fine presentation of a well analyzed series. A long-term study such as this one gives us an opportunity to examine not only pathologic prognostic factors, but also the results of treatment. As we all know, treatment has changed remarkably over the long period of time covered in this study.

At the University of Alabama we have recently completed the ten-year analysis of a prospective randomized trial comparing modified and radical mastectomy. The results of this trial show that there has been a significant reduction in local recurrence when radical mastectomy is utilized for patients with T2 tumors and clinically palpable nodes and patients with T3 cancers.

It would be interesting to know whether any such benefit has been observed for patients treated with radical mastectomy *versus* modified radical mastectomy in the Tulane series.

DR. EDWARD T. KREMENTZ (New Orleans, Louisiana): I wish to compliment Drs. Sutherland and Mather on their detailed analysis of the Charity Hospital Tumor Registry data on breast cancer. The material will be important for future study and treatment of breast cancer. It also counteracts much of the "therapeutic nihilsm" regarding the surgical treatment of breast cancer that is being fostered by some of our medical colleagues.

In this centennial year, I wish to comment on the part that members of the Southern Surgical Association have played in the development of the Tumor Registry at Charity Hospital. The Registry was started in 1948 as a result of activities of a coordinating committee of the Louisiana Division of the American Cancer Society, and was composed of faculty members from The Louisiana State University (L.S.U.) and Tulane. The three major persons involved were Dr. Ambrose Storch of Tulane, Dr. James Rives of L.S.U., and Dr. Alton Ochsner of Tulane, who obtained funding from the Louisiana Division of the American Cancer Society to start a registry of cancer patients at Charity Hospital.

By 1952, the simple card file system had become unworkable. Dr. Walter Burdette of the L.S.U. faculty initiated action to establish a formal Tumor Registry Board and obtained support for this activity from the Cancer Society and other involved organizations. Drs. C. Hammond and C. Aubrey Schneider of the American Cancer Society National Office in New York City came to New Orleans to reorganize our data collection system and put the registry on a sound statistical basis.

The original board included Dr. Rawley Penick and Dr. Burdette, who served as Chairman; the Director of Charity Hospital, a representative from the Louisiana Health Department, and myself. All three surgeons were or became members of the Southern Surgical Association.

In 1955, Walter left to become Chairman of Surgery at Missouri, and I was elected Chairman of the Registry. The Board found outside sources to fund the majority of the Registry's activities until the middle 1970's. During this time, nine of the 40 board members have been S.S.A. members. In 1981, a bill was initiated in Louisiana to use cigarette tax money to support cancer control activities, and since then, those funds have supported the Charity Hospital Tumor Registry. This legislation was the result of activities started by Dr. Robert Beazley of L.S.U. and other persons active in cancer control activities, including my associate at Tulane, Dr. R. Davilene Carter.

Our Registry at Charity Hospital is remarkable in that it now contains over 67,000 cancer case entries, all of them computerized and available for statistical analysis by Charity staff members. Sixty-five per cent of the cases are black patients, and 35% of the cases are white. There are all sorts of interesting data for analysis in the computer banks. For instance, in my field of interest, there are over 100 cases of melanoma in black patients, which is the largest number reported from a single hospital in North America.

Faculty members at Tulane and L.S.U. have published approximately 400 publications utilizing data produced by the Tumor Registry. The 39-year data collection has been carried out by three Registrars: Mrs. Marian Wogon, Mrs. Brent Robertson and Mrs. Jane Rodriguez, who have been aided by a very dedicated group of helpers. The role of Louisiana members of the SSA has been and will continue to be an important part of cancer control studies at Charity Hospital and in the state of Louisiana.

DR. CARL M. SUTHERLAND (Closing discussion): I would like to thank all of the discussants for their interest, comments, and questions.

Numerous questions were presented by Drs. Copeland, Pigott, and Urist on treatment-related variables. In this study we did not analyze using treatment variables.

To answer Dr. Humphrey's question about one's being able to analyze for local recurrences related to type of therapy, in the future, I or any other Charity Hospital staff member will be able to perform this analysis. It will certainly be a good study, and will yield additional data on local recurrence factor.

To reply to Dr. Humphrey's question regarding the similarity of survival between the group of patients being clinically node-negative with fixation and those clinically node-positive without fixation, an overall trend occurs; that is, as the important factors increase in number and severity, the stage increases while differences between the various groups decrease, and an overall poorer and more uniform survival occurs as the accumulation of those important factors increases. However, the relationship of those factors to each other, as well as what the biologic factors are, is unclear. In any of these prognostic factor studies that we perform, we can study only the clinical factors. The underlying biologic factors causing these clinical factors are unknown and require additional study.

That same comment applies, to some extent, to Dr. Beazley's question about findings of peau d'orange, which is a clinical manifestation of an underlying biologic process. Again, I would like to emphasize that peau d'orange is related to stage. If a prognostic factor study is conducted in any group of patients, and if a factor is related to the stage of disease being studied and that stage of disease is restricted, then the analysis may become confounded. While a study restricted to a stage is valid for that study, entirely different results are possible when additional stages are included.

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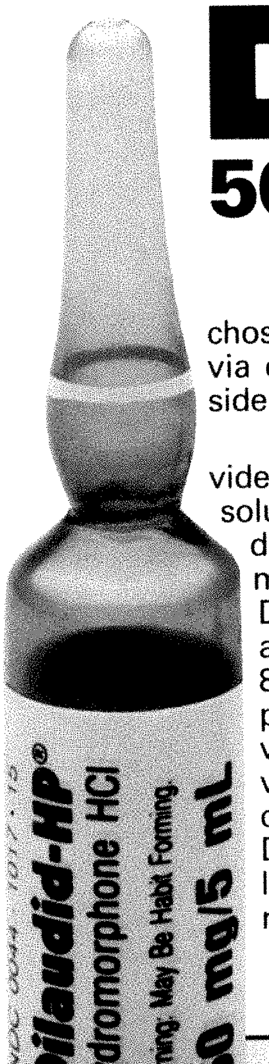

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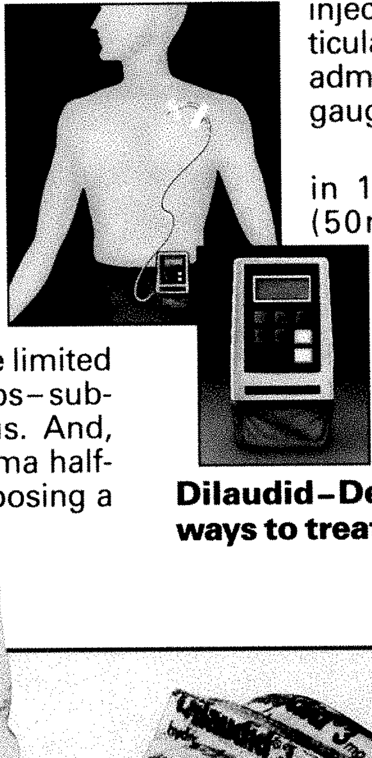

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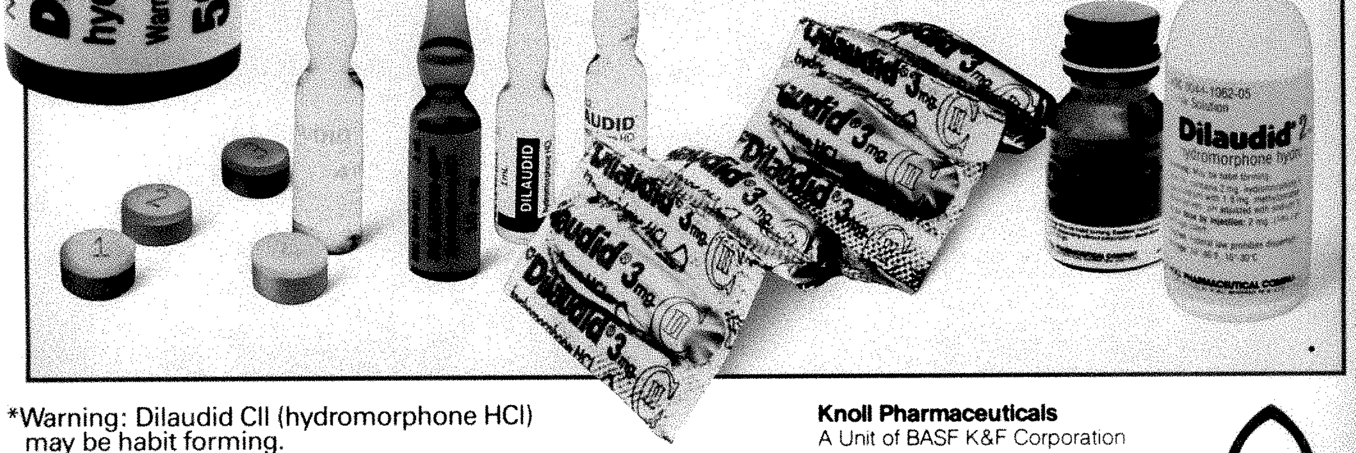

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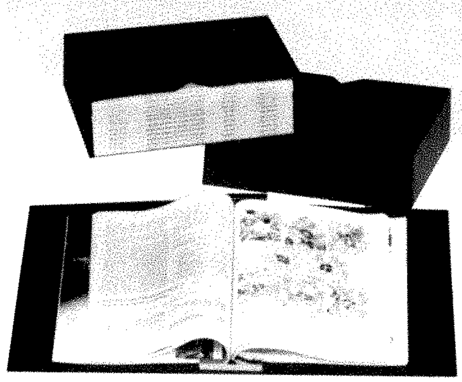

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Splenectomy in Hematologic Disorders

The Ever-changing Indications

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A comparison between a series of splenectomies performed at the University of Virginia Medical Center for hematologic disorders between 1946 and 1962 (Series I) and 1963 and 1982 (Series II) is presented. Four hundred splenectomies (20 per year) were performed between 1963 and 1982 compared with 94 (5.5 per year) between 1946 and 1962. Also noted in Series II was a sharp decline in the number performed each year between 1974 and 1983. The major factor responsible for these observations was the evolution of the staging laparotomy for malignant lymphomas, particularly Hodgkin's disease, and the decline in the average annual incidence of staging laparotomies since 1974. Staging laparotomy currently is rarely done for non-Hodgkin's lymphomas. Also contributing to the changes noted was an increase in the total number but subsequent fall in the annual incidence of splenectomy for hereditary spherocytosis, idiopathic hypersplenism, and myeloproliferative disorders in Series II. The average number of splenectomies for idiopathic thrombocytopenic purpura increased from 1.1 per year in Series I to 3.6 per year in Series II; the annual incidence during the study period of Series II, however, remained constant. The total number of splenectomies for hairy cell leukemia and Felty's syndrome increased from zero in Series I to 12 and 17, respectively, in Series II, whereas the number of miscellaneous reasons dropped from 29 (1.7 per year) in Series I to 15 (0.75 per year) in Series II. The mortality rate in Series I was 6.3% compared with 4.0% in Series II. No deaths occurred in Series II after 1979. Indications for splenectomy in Series II were for diagnostic purposes in 3.2%, therapeutic in 56.5%, staging in 39.5%, and restaging in 0.8%. Accessory spleens were found in 49 (12.5%) in Series II.

THE INDICATIONS FOR splenectomy in hematologic disorders have changed considerably over the past two decades. These changes have occurred mainly as a result of the evolution of the staging laparotomy to evaluate patients with Hodgkin's disease[1,2] and, to a lesser extent, non-Hodgkin's lymphomas.[3-5] Also contributing to this change has been the decline in the number of patients who require splenectomy for diagnostic purposes and a change in the indications for splenectomy.[5] To assess the impact of these and other factors on the indications and frequency of splenectomy for hematologic disorders, a retrospective review of all splenectomies at the University of Virginia Hospital over a 20-year period from 1963 to 1982 (Series II) was done and compared with an older series reported from the same institution from 1949 to 1962 (Series I).[6]

Materials and Methods

All splenectomies performed at the University of Virginia Hospital between January 1, 1963 and December 31, 1982 were reviewed. The indication for splenectomy was categorized as either therapeutic, diagnostic, or as a part of a staging or restaging laparotomy for malignant lymphomas. Included were several well-defined hematologic diseases, Felty's syndrome, cases of hypersplenism with nonspecific histopathologic findings in the spleen (idiopathic hypersplenism or primary splenic hyperplasia), and a miscellaneous group of disorders such as storage diseases, sarcoidosis, primary splenic tumors and malformations, and histiocytosis X (idiopathic histiocytosis).

A histopathologic review of all staging splenectomies, most of which were done as a part of a previous study,[2] all diagnostic splenectomies, and all splenectomies performed for idiopathic hypersplenism was performed. The morbidity and mortality rates for each subgroup

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TABLE 1. *Indications for Therapeutic Splenectomy in Hematologic Disorders**

- Anemia
- Thrombocytopenia
- Granulocytopenia
- Hypermetabolism
- High output cardiac decompensation
- Mechanical compression of the stomach with early satiety
- Recurrent painful splenic infarcts
- Bleeding esophageal or gastric varices (rare)

*Modified from Hess CE.[5]

and for the entire series were also evaluated. Any death or complication occurring within 30 days after splenectomy or during the hospitalization for the splenectomy, regardless of the length of stay, was considered an operative event.

Therapeutic Splenectomy

Indications for therapeutic splenectomy varied considerably depending on the nature of the underlying disorder and the size of the spleen. In Table 1, the various factors that contributed to a decision to perform a therapeutic splenectomy are listed.[5] In many cases, a combination of these factors was present. Patients with massive splenomegaly, regardless of cause, usually manifested most of the abnormal findings listed in Table 1. Such patients often are referred to as having the "big spleen syndrom".[5,7] In patients with myeloproliferative disorders, chronic lymphocytic leukemia, hairy cell leukemia, and idiopathic hypersplenism, splenectomy was recommended because of a varying degree of the "big spleen syndrome."

In the majority of therapeutic splenectomies, however, the nature of the underlying disorder was a major factor in the decision to recommend splenectomy.

Idiopathic Thrombocytopenic Purpura

During the first 10 years of this study, splenectomy usually was performed in patients who either did not respond to a 4-week course of oral prednisone (a rise in platelet count of less than 25,000/mm^3 above pretreatment levels), or repeated relapse after either a good response (rise in platelet count of greater than 50,000/mm^3) or an excellent response (rise in platelet count of 100,000/mm^3 or greater to a level of 150,000/mm^3 or greater).[8] In the last 10 years of the study, many patients also had failed to respond to other therapeutic modalities including androgens and one or more cytotoxic agents.

In the current study, response to splenectomy was evaluated at 2–4 weeks after splenectomy. An excellent or complete response was defined as a rise in the platelet count of 100,000/mm^3 or more above preoperative values, a good or partial response was a rise of 50,000–100,000/mm^3 above preoperative values, and a failure as a rise of less than 50,000/mm^3 above preoperative values.

Hereditary Spherocytosis

Traditionally, splenectomy has been recommended in all adults and older children (above the age of 3 years) with a diagnosis of hereditary spherocytosis because of the risk of development of gallstones, aplastic crisis, and the possible late development of hemachromatosis.[9] Aplastic crisis has proven to be an unusual event, particularly in mild cases, and the late development of hemachromatosis has been challenged.[10] As a result, during the latter part of this study, splenectomy has not been recommended in mild cases. Hematocrit values to evaluate response were recorded at 2–4 weeks after splenectomy.

Felty's Syndrome

Splenectomy was recommended for patients with neutropenia, usually severe, and recurrent or resistant infections.[11] In more recent years, failure to respond to a trial of gold therapy often preceded the recommendation for splenectomy.

Autoimmune Hemolytic Anemia

Splenectomy was recommended for patients who either did not respond to a 2–4-week course of oral prednisone, or who repeatedly relapsed after an initial good or excellent response to prednisone.[9] Hematocrit values to evaluate response were recorded at 2–4 weeks after splenectomy.

Thrombotic Thrombocytopenic Purpura

Before the established efficacy of plasmapheresis in thrombotic thrombocytopenic purpura,[12] which occurred during the period covered by this study, splenectomy was recommended as a part of the initial therapy of this disorder.[13] Splenectomy is now recommended only in patients who fail plasmapheresis or continue to relapse when plasmapheresis is discontinued.

Diagnostic Splenectomy

A diagnostic splenectomy was performed in one or more of the following clinical settings: (1) a splenic tumor or defect usually demonstrated by one or more imaging techniques or angiography, (2) fever of unknown origin with or without splenomegaly after an exhaustive investigation failed to reveal a definitive diagnosis, and (3) massive splenomegaly with varying elements of the "big spleen syndrome"; in most of these

TABLE 2. *Splenectomy for Hematologic Disorders*

	Series I 1946–62		Series II 1963–82	
	No.	%	No.	%
Hodgkin's disease	4	4.3	137	34.3
Non-Hodgkin's lymphoma	5	5.3	35	8.7
Idiopathic thrombocytopenic purpura	18	19.1	72	18.0
Hereditary hemolytic anemia	19	20.2	45	11.2
Idiopathic hypersplenism	0	0.0	14	3.2
Cirrhosis with portal hypertension	6	6.3	*	*
Myeloproliferative disorders	7	7.4	32	8.0
Autoimmune hemolytic anemia	5	5.3	8	2.0
Hairy cell leukemia	0	0.0	12	3.0
Felty's syndrome	0	0.0	17	4.2
Chronic lymphocytic leukemia	1	1.0	7	1.75
Thrombotic thrombocytopenia purpura	0	0.0	6	1.5
Miscellaneous	29	30.8	15	3.7
Total	94		400	

* This group was not included in the current series.

cases a therapeutic indication also existed. In many cases of idiopathic hypersplenism, a diagnostic component was present.

Staging Laparotomy

Since 1969, the indications for a staging laparotomy for Hodgkin's disease at the University of Virginia Hospital have remained essentially unchanged.[2,14] All patients who were considered operable candidates with clinical stage I-IIA and B, I-IIEA and B, and many with clinical stage IIIA disease, were recommended for staging laparotomy.

The indications for staging laparotomy in non-Hodgkin's lymphomas changed dramatically during this study period. For approximately 7 years, from 1970 to 1977, patients with non-Hodgkin's lymphoma who were considered candidates for radiotherapy alone for curative intent were recommended to undergo a staging laparotomy.[14] Most of these patients had clinical stage I-IIA disease. Over the last 5 years of the study, a staging laparotomy usually was not recommended even in patients who were considered candidates for radiotherapy alone for curative intent.

Restaging Laparotomy

A restaging laparotomy to include a splenectomy, when appropriate, was recommended for patients with residual lymphadenopathy or splenic tumors or defects after the completion of definitive therapy, either radiotherapy, combination chemotherapy, or both, in patients with Hodgkin's disease and non-Hodgkin's lymphoma.[15]

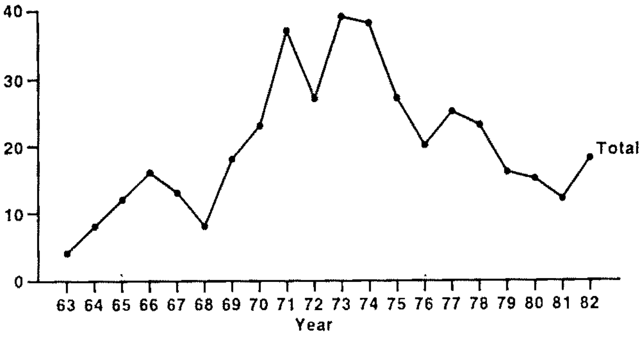

FIG. 1. Annual incidence of splenectomy for hematologic disorders: 1963–1982.

Results

In Table 2 are the number and relative frequency of the various hematologic disorders for the 20-year period, 1963–1982 (Series II), covered by this study along with a comparison with the previous report from this institution covering a 17-year period, 1946–1962 (Series I).[6] Patients with congestive splenomegaly secondary to intrinsic liver diseases were excluded from the current study. The actual number of splenectomies performed each year for all hematologic disorders is shown in Figure 1. A breakdown as to the major reason for performing the splenectomy is shown in Table 3. Accessory spleens were found in 49 (12.5%) of cases in Series II.

Morbidity and Mortality

The morbidity and mortality, overall and for each major diagnostic subgroup, are summarized in Table 4. In the three patients in whom a pulmonary embolus developed, only one had thrombocytosis (platelet count 819,000/mm^3) after a splenectomy for ITP in whom a pulmonary embolus occurred on the tenth postoperative day.

No operative deaths were observed in the 136 patients who underwent staging laparotomy for Hodgkin's disease (Table 4). The only death occurred in the one therapeutic splenectomy done in 1963, a 23-year-old man with massive splenomegaly.

Of the two deaths in the idiopathic thrombocytopenic purpura group, one, a 66-year-old man, died of gastroin-

TABLE 3. *Hematologic Disorders: Indications for Splenectomy 1963–1982*

	No.	%
Diagnostic	13	3.2
Therapeutic	226	56.5
Staging	158	39.5
Restaging	3	0.8
Total	400	

TABLE 4. *Morbidity and Mortality in Patients Undergoing Splenectomy for Hematological Diseases**

	HD (N = 137)	NHL (N = 35)	ITP (N = 72)	HHA (N = 45)	IH (N = 14)	MPD (N = 32)	AIHA (N = 8)	HCL (N = 12)	FS (N = 17)	CLL (N = 7)	TTP (N = 6)	MISC† (N = 15)	Total (N = 400)
Mortality	1 (0.7%)	0	2 (2.8%)	0	0	4 (12.5%)	0	0	2 (11.8%)	0	5 (83%)	2 (13.3%)	16 (4%)
Morbidity													
Pneumonia	5	1	1	1	0	5	2	0	1	1	1‡	0	18 (4.7%)
Wound infection	3	1	3	2	0	1	0	0	1	1	0	1	13 (3.4%)
Subphrenic abscess	2	2	0	0	0	2	0	0	0	0	0	0	6 (1.6%)
Pleural effusion	2	2	1	0	0	0	0	0	1	0	0	0	6 (1.6%)
Postoperative hemorrhage	0	0	2	0	0	2	0	0	1	0	0	0	5 (1.3%)
Pulmonary embolus	0	0	1	0	0	0	0	0	0	0	1‡	1	3 (0.8%)
Urinary tract infection	0	1	0	1	0	0	0	0	0	0	0	0	2 (0.5%)
Small bowel obstruction	0	0	0	0	0	1	1	0	0	0	0	0	2 (0.5%)
Total morbidity	12 (8.8%)	7 (20%)	8 (11.4%)	4 (8.9%)	0	11 (39.3%)	3 (37.5%)	0	4 (26.7%)	2 (28.6%)	2 (100%)	2 (15.4%)	54 (13.5%)

* 30-day and/or in-hospital morbidity and mortality.

† Miscellaneous group includes idiopathic histiocytosis, storage diseases, hamartomas, sarcoidosis, acute leukemia, nephrotic syndrome, myelodysplastic syndrome, and aplastic anemia.

‡ Complications occurred in same patient.

HD = Hodgkin's disease; NHL = non-Hodgkin's lymphoma; ITP = idiopathic thrombocytopenic purpura; HHA = hereditary hemolytic anemia; IH = idiopathic hypersplenism; MPD = myeloproliferative disorder; AIHA = autoimmune hemolytic anemia; HCL = hairy cell leukemia; FS = Felty's syndrome; CLL = chronic lymphocytic leukemia; TTP = thrombotic thrombocytopenic purpura; MISC = miscellaneous group

testinal hemorrhage and renal failure on postoperative day 1; the other, a 19-year-old female, died on the third postoperative day of respiratory failure.

Two of the four deaths in the myeloproliferative disorder group were from sepsis, one on postoperative day 24 and one on day 7. A third patient died of cardiopulmonary arrest on the day of the operation, and the fourth died on day 17 of a pulmonary embolus and pneumonia.

One of the two deaths in the Felty's syndrome group, a 60-year-old man, was due to cardiac arrest on postoperative day 3; the second, a 66-year-old woman, died on day 21 of undetermined cause.

All five deaths in the group with thrombotic thrombocytopenic purpura were due to progression of their disease.

One of the two deaths in the miscellaneous group was a 66-year-old man with acute leukemia and massive splenomegaly who died with disease progression on postoperative day 30; the other patient, a 69-year-old woman with malignant histiocytosis, died on postoperative day 12 of sepsis. No operative deaths occurred since 1979.

Hodgkin's Disease

All patients underwent splenectomy for staging except one patient who underwent splenectomy for Hodgkin's disease. The mean age was 28.4 years (range: 7–72 years), and the male:female ratio was 0.93:1. In 44 patients (32.1%), the spleen was positive for Hodgkin's disease. The mean weight of positive spleens was 403.3 g (range: 70–2090 g) compared with 207.5 g (range: 50–489 g) for negative spleens. Accessory spleens were found in 20 patients (14.6%). In Figure 2 the actual number of splenectomies performed each year for staging of Hodgkin's disease is compared with the actual number of splenectomies performed each year for all hematologic disorders.

Non-Hodgkin's Lymphomas

Of the 35 splenectomies in this group, 22 were for staging, three were for restaging, three were diagnostic, and six were therapeutic. A comparison of the actual number of splenectomies performed each year for staging laparotomy in non-Hodgkin's lymphomas and the actual number of splenectomies performed each year for all hematologic disorders is shown in Figure 3.

Idiopathic Thrombocytopenic Purpura

The actual number of splenectomies performed each year for idiopathic thrombocytopenic purpura is compared with the actual number of splenectomies performed each year for all hematologic disorders in Figure

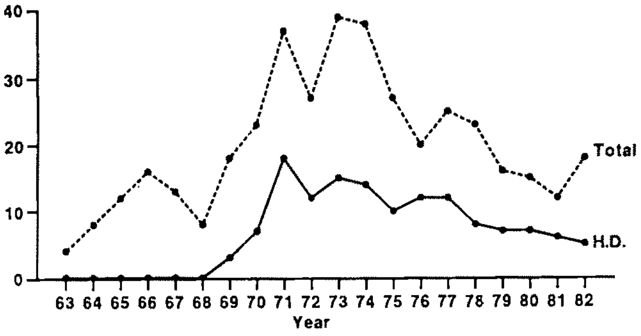

FIG. 2. Comparison between the annual incidence of splenectomy for staging of Hodgkin's disease (HD) and the incidence of splenectomy for all hematologic disorders: 1963–1982.

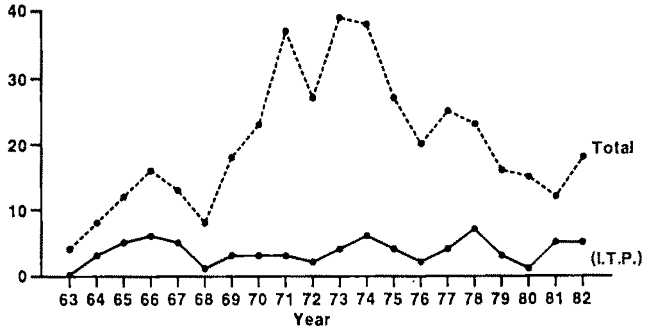

FIG. 4. Comparison between the annual incidence of splenectomy for idiopathic thrombocytopenic purpura (ITP) and the incidence of splenectomy for all hematologic disorders: 1963–1982.

4. An excellent response was observed in 83%, a good or partial response was observed in 6%, and a poor response was observed in 11%. The mean platelet count was 46,890/mm^3 before operation and 409,980/mm^3 after operation. The mean splenic weight was 160 g (range: 22–530 g), the mean age was 35.7 years (range: 2–76 years), and the male:female ratio was 1:1.84. There were two deaths (2.7%). Accessory spleens were found in eight patients (11.2%).

Hereditary Hemolytic Anemia

Of the 45 splenectomies in this group, 39 were for hereditary spherocytosis, four for hemoglobinopathies, and two for enzymopathies. A comparison of the actual number of splenectomies performed each year for hereditary spherocytosis to the actual number of splenectomies performed each year for all hematologic disorders is shown in Figure 5. Only one splenectomy has been performed for hereditary spherocytosis since 1976. In the hereditary spherocytosis group, the mean age was 14 years (range: 8 months–48 years), the male:female ratio was 1:1.24, the mean splenic weight was 381 g (range: 30–1580 g), mean hematocrit increased to 38% from 29% before operation, mean reticulocyte count decreased from 13.1% to 2.1% after operation, and 12 (30.7%) accessory spleens were found.

Idiopathic Hypersplenism

Of the 14 cases, seven were for diagnostic and seven were for therapeutic reasons. A comparison of the actual number performed each year with that of all hematologic disorders is shown in Figure 6. The mean age was 45 years (range: 2–66 years), the male:female ratio was 3.67:1, and the mean splenic weight was 722 g (range: 200–2700 g). In the seven splenectomies performed for therapeutic reasons, a significant rise in either the hematocrit, white blood cell count, or platelets occurred in all patients at 2–4 weeks after splenectomy.

Myeloproliferative Disorders

In this group, 24 patients had myelofibrosis with myeloid metaplasia, and eight had chronic myelocytic leukemia. A comparison of the actual number each year with the actual number each year of all hematologic disorders is shown in Figure 7. In the myelofibrosis group the mean age was 59.2 years with a male:female ratio of 2.1:1. The mean hematocrit was 31% before

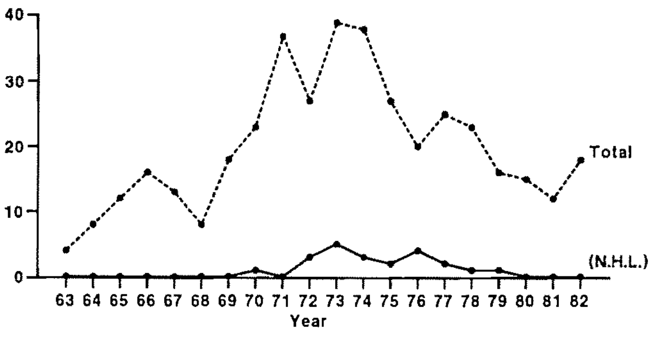

FIG. 3. Comparison between the annual incidence of splenectomy for staging of non-Hodgkin's lymphoma (NHL) and the incidence of splenectomy for all hematologic disorders: 1963–1982.

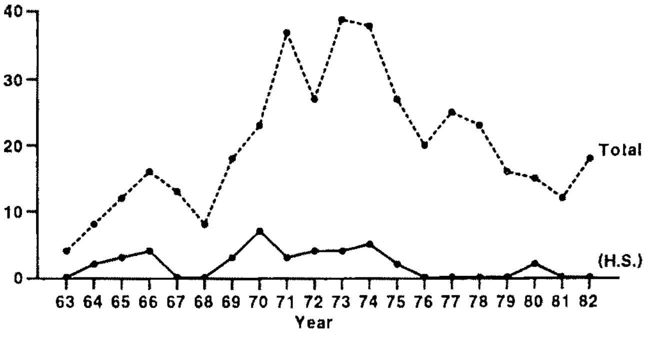

FIG. 5. Comparison between the annual incidence of splenectomy for hereditary spherocytosis (HS) and the incidence of splenectomy for all hematologic disorders: 1963–1982.

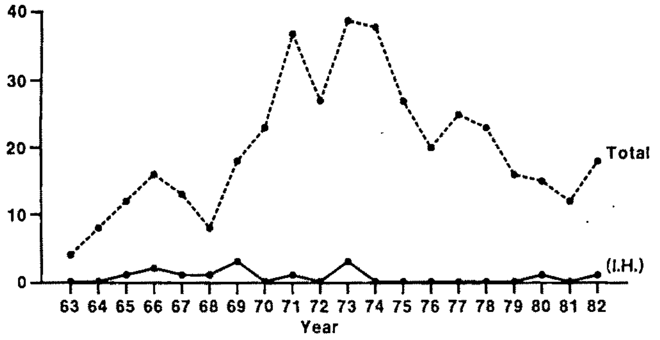

FIG. 6. Comparison of the annual incidence of splenectomy for idiopathic hypersplenism (IH) and the incidence of splenectomy for all hematologic disorders: 1963–1982.

operation and 44% at 2–4 weeks after operation; the mean platelet count was 103,000/mm³ before operation and 212,670/mm³ at 2–4 weeks after operation. The mean splenic weight was 1999 g (range: 640–4400 g). Four (16%) accessory spleens were found. For the eight cases of chronic myelocytic leukemia, the mean splenic weight was 1900 g (range: 332–4300 g), the mean age was 36 years (range: 2–71 years), and the male:female ratio was 3:1. One accessory spleen (13%) was found.

Autoimmune Hemolytic Anemia

The mean age for the eight patients in this group was 54.5 years (range: 21–68 years) and the mean splenic weight was 389 g (range: 253–560 g). The mean preoperative hematocrit was 26% (range: 19–35%), compared with a mean postoperative hematocrit at 2–4 weeks of 44% (range: 30–53%). No accessory spleens were found.

Hairy Cell Leukemia

Eleven of the 12 splenectomies in this group were performed for therapeutic reasons. The mean age was 52 years (range: 39–64 years), the mean splenic weight was 1467.3 g (range: 786–2330 g), and one accessory spleen (8.3%) was found.

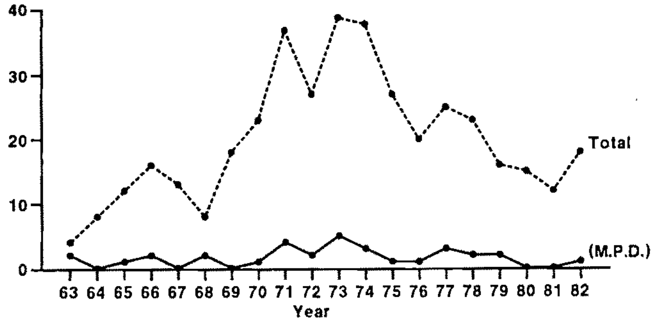

FIG. 7. Comparison of the annual incidence of splenectomy for myeloproliferative disorders (MPD) and the incidence of splenectomy for all hematologic disorders: 1963–1982.

Felty's Syndrome

The mean age of the 17 patients in this group was 58 years (range: 37–70 years), the male:female ratio was 1:43.1, and the mean splenic weight was 653 g. The mean white blood cell count was 2256/mm³ before operation and 7712/mm³ at 2–4 weeks after operation. Two accessory spleens (11.8%) were found.

Chronic Lymphocytic Leukemia

All seven cases were for therapeutic reasons. The mean splenic weight was 2946.6 g (range: 1420–4790 g). Only one has been done since 1978.

Thrombotic Thrombocytopenic Purpura

Splenectomy was performed as a part of the initial therapy in all of these patients, and five died in the postoperative period.

Miscellaneous

Splenectomy in all 15 patients in the group was performed for therapeutic and/or diagnostic reasons. Three were for splenic hamartomas, three for storage diseases (2 Gaucher's disease, 1 sea blue histiocyte syndrome), two for sarcoidosis, two for idiopathic histiocytosis (1 histiocytosis X, 1 malignant histiocytosis), two acute leukemias, one with nephrotic syndrome and intra-abdominal lymphadenopathy (findings were non-specific), one myelodysplastic syndrome, and one aplastic anemia (Fanconi's type).

Discussion

The average number of splenectomies performed each year for hematologic disorders during the 20-year period, 1963–1982 (Series II), covered by this retrospective study was 20 per year compared with only 5.5 per year over a 17-year period, 1949–1962 (Series I), in a previous report from this institution (Table 2).[6] When the actual number of splenectomies performed each year during this study was plotted, a marked increase occurred in 1969, peaking in 1971, 1973, and 1974 (Fig. 1). Since 1974, except for a slight increase in 1977 and 1982, there has been a steady decrease in the number of splenectomies performed each year (Fig 1). These changes have been the result of several important factors.

The impact of the staging laparotomy for malignant lymphomas, especially for Hodgkin's disease[1,2] was by far the most important factor. Beginning in 1969 (Fig. 2), the year the first staging laparotomy for Hodgkin's disease was performed at the University of Virginia Hospital,[2] the marked increase and subsequent decline in the number of laparotomies performed paralleled the rise and fall in the total number of splenectomies done (Fig. 2).

The decline in the number of staging laparotomies for Hodgkin's disease since 1974 is multifactorial, but may be due mainly to the changes in referral pattern observed over the past few years. Several private hematologists, oncologists, and radiotherapists have established practices in our referral area since 1975, and care for an increasing number of patients with malignant lymphomas.

Other factors have also contributed to the decline. Most patients with clinical stage IIIA disease, particularly those with $IIIA_2$ disease who would have been considered candidates for a staging laparotomy during the early 1970s, no longer are recommended to undergo a laparotomy.[14] Such patients are now treated with combination chemotherapy alone with or without supplemental radiotherapy as the initial curative therapy. A similar change occurred in our approach to patients with very large mediastinal masses (greater than one third of the diameter of the chest), especially if B symptoms are present.[14]

Although to a lesser degree, the emergence and essential disappearance of the staging laparotomy for non-Hodgkin's lymphomas during this study period has had an impact similar to that of the staging laparotomy for Hodgkin's disease on the annual incidence of splenectomies (Fig. 3). Only a rare staging laparotomy is currently recommended even in the few patients who are considered candidates for radiotherapy alone for curative intent.[14] No staging laparotomies have been performed since 1979 (Fig. 3).

The sharp increase in the average number of splenectomies performed each year for other hematologic disorders in Series II (Table 2), and the changes observed when the actual number performed for each disorder was plotted also were important factors.

The average number per year for idiopathic thrombocytopenic purpura increased from 1.1 in Series I to 3.5 in Series II (Table 2), for hereditary hemolytic anemia increased from 1.1 in Series I to 2.3 in Series II, for myeloproliferative disorders increased from 0.4 in Series I to 1.6 in Series II, for hairy cell leukemia increased from none in Series I to 0.6 in Series II, for Felty's syndrome increased from none in Series I to 0.8 in Series II, for chronic lymphocytic leukemia increased from 0.06 in Series I to 0.35 in Series II, and for thrombotic thrombocytopenic purpura increased from none in Series I to 0.3 in Series II (Table 2). Less splenectomies were performed for miscellaneous reasons in Series II, 0.75 per year *versus* 1.7 in Series I (Table 2). Patients with congestive splenomegaly secondary to hepatic cirrhosis were not included in Series II.

When the actual number of splenectomies performed annually for each disorder was plotted, only the idiopathic thrombocytopenic purpura group remained essentially the same throughout the study period (Fig. 4). In the hereditary spherocytosis group, a drop occurred after 1974 (Fig. 5), in the idiopathic hypersplenism group, a drop occurred after 1973 (Fig. 6), and in the myeloproliferative disorder group, a drop occurred after 1979.

The steady rate of splenectomies performed for idiopathic thrombocytopenic purpura is indicative of the fact that a significant number of such patients still require splenectomy for control of their disease.[8,16-18]

The change observed in the spherocytosis group probably was the result of the change in our policy regarding splenectomy in this disorder,[9] and possibly a change in referral pattern. Splenectomy is not currently recommended for mild cases.

In the case of idiopathic hypersplenism, improved technology, especially the availability of new imaging techniques and fine needle aspiration of intra-abdominal lymph nodes and masses, has improved tremendously our diagnostic capability in patients with fever of unknown origin with or without splenomegaly and in patients with splenomegaly in general.[5] The same reasons probably account for the very low percentage (3.2%) of diagnostic splenectomies in this study (Table 3). A diagnostic splenectomy probably should not be performed in relatively asymptomatic patients with splenomegaly, even with a varying degree of peripheral cytopenia, if a systematic and exhaustive evaluation fails to elucidate a cause.[5] A liver biopsy to rule out intrinsic liver disease should precede any decision to recommend a splenectomy in such patients. In the absence of intrinsic liver disease, splenectomy frequently reveals only nonspecific histopathologic changes. The only exception is when a splenic defect or tumor mass is noted on imaging.

The only apparent explanation for the decrease in the number of therapeutic splenectomies for myeloproliferative disorders is a change in referral pattern; there have been no advances in other treatment modalities.

The overall mortality rate of 4% and morbidity rate of 13.5% (Table 4) are comparable to several other large series of splenectomies for hematologic disorders.[6,19-23] The very high mortality rate of 83% (Table 4) in patients with thrombotic thrombocytopenic purpura (representing 31% of the deaths in this series) is similar to other reports where splenectomy is performed as a part of the initial therapy for this disorder.[12,13] With the marked improvement in survival observed with plasmapheresis,[12] splenectomy is now recommended only in patients who do not respond or who continue to relapse after stopping pheresis.

The zero mortality rate in staging laparotomies, both in Hodgkin's disease and non-Hodgkin's lymphoma, the overall low morbidity rate, and absence of a mortality in any case between 1979 and 1983 continue to support the acceptability of the risk of splenectomy in selected patients with hematologic disorders.

The results of this review when compared with an older study from the same institution establish that the indications for splenectomy in hematologic disorders continue to change. Although diagnostic splenectomy is currently an unusual indication for splenectomy, therapeutic splenectomy remains the treatment of choice for a variety of well-defined clinical and laboratory manifestations in several hematologic disorders. Splenectomy as a part of a staging laparotomy for Hodgkin's disease is still indicated in the great majority of patients who are considered candidates for radiotherapy alone for curative intent. Splenectomy as a part of a restaging procedure to evaluate residual tumor masses or defects is indicated in some patients with Hodgkin's disease and non-Hodgkin's lymphoma.

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DISCUSSION

DR. HENRY LAWS (Birmingham, Alabama): I would like to compliment Dr. Wilhelm and his colleagues on their excellent results in these diverse and often very complicated problems. Dr. Wilhelm asked us to discuss the paper because we managed 130 of these patients with hematologic disorders, not Hodgkin's staging, over a 12-year period with seven deaths.[1] Four of these patients died with overwhelming sepsis in the early postoperative period, usually with a very low, absolute granulocyte count. I would caution everyone to be concerned about operating on individuals of this nature with a granulocyte count below 100 or 200, even though the total white cell count may be several thousands.

Recently, we had occasion to do a splenectomy on an AIDS patient with cryptococcal meningitis, and very severe leukopenia and thrombocytopenia in the course of his disease. The severe leukopenia would not allow therapy with Retrovir. (Slide) This has also been observed by other individuals. Splenectomy afforded a dramatic increase in both the white count and the platelet count. On the other hand, when the AZT therapy was reinstituted, the white count promptly became too low to be tolerable again. I doubt that splenectomy was of any real benefit to this patient.

I would like to ask Dr. Wilhelm and Dr. Jones several questions. Of the patients who died, did severe granulocytopenia play a part? Are there any patients with early Hodgkin's Disease, for instance, Stage I or II on the right side, upper body, that you might not stage? What postoperative management or prophylaxis do you recommend for patients after splenectomy to avoid sepsis? Have you had any experience in the treatment of AIDS patients, and do you anticipate splenectomy to play any part in these individuals?

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DR. NORMAN HALPERN (Birmingham, Alabama): Studies such as this one remind us that concepts of management of certain disorders can change substantially over time.

As Dr. Wilhelm indicated, this can be due not only to variations in referral patterns and development of presumably superior nonsurgical diagnostic and therapeutic options, but also to the eventual recognition that surgical management may, indeed, be highly effective in certain clinical settings.

We should also remember that there may be a good bit of variation in practice patterns between institutions.

(Slide) This is a slightly different time period at UAB than what Dr. Laws referred to, and reviews a 12-year experience up to 1985.

The most profound change in our clinical practice from the earlier to later years of this study was a dramatic decrease in the number of splenectomies for trauma. Operations for hematological disorders generally increased. Those for Hodgkin's staging showed a slight decline.

(Slide) Over the past six years I have had the privilege of being involved in nearly all of the splenectomies for hematologic disease at UAB, and I thought it would be of interest to compare this most recent experience with Dr. Wilhelm's later series. Using the data available from the program abstract, it would appear that there certainly are some differences.

There is a slight difference in the duration of the time frame, but I think we can make some contrasts with the numbers.

With Hodgkin's staging, however, our experiences are similar, and both show a somewhat declining yearly incidence. In our case, I suspect it is a matter of the patients' being managed elsewhere since our hematologists generally favor a policy of operative staging.

In a similar way, they have not been impressed with the results of gamma globulin or other recently promoted drugs for immune thrombocytopenia, so we are still seeing about eight or nine of those yearly.

Dr. Wilhelm, you show a large volume of patients with hereditary spherocytosis. In our system, children are cared for in a separate hospital. Were many of your spherocytosis patients in the pediatric group? You mentioned that operation was becoming less frequent for that indication, but when you do find the indication, what age guidelines would you suggest for splenectomy?

Another interesting difference was in the management of non-Hodgkin's lymphoma. All of our operations were for correction of hypersplenism or for diagnosis of splenomegaly, whereas at your institution, over half of yours used to be for staging. I had a question on the role of operative staging for non-Hodgkin's lymphomas, but you clarified it in your discussion.

In general, we have been quite satisfied with the results of splenectomy for selected patients with the various leukemias or myelofibrosis, realizing, of course, that operation is just a component of their overall therapy and that certainly more risk is involved with operation. Nevertheless, removal of a symptomatic, massively enlarged or hyperfunctioning spleen can contribute greatly to an improved quality of survival for these people.

I envy your experience with Felty's Syndrome. Your referral patterns are remarkably different from ours in that category.

Finally, in the miscellaneous group I have included our eight patients with thrombotic thrombocytopenia purpura, an interesting disorder that seems to be (at least in our institution) a bit more frequent recently. As your comment indicated, I think plasmapheresis has made a difference. Of those eight patients with TTP having splenectomy, all eight survived. Nevertheless, we still have a bit of difficulty defining the criteria that would indicate plasmapheresis has filled. Perhaps you could give us your thoughts on that.

Dr. Lazar J. Greenfield (Ann Arbor, Michigan): I would like to congratulate Dr. Wilhelm and his associates for their results and for his excellent presentation.

This is an area that has been of considerable interest to Dr. William Coon of our faculty, who is an acknowledged expert. Since I am not an expert, I would like simply to ask two questions.

First, was there any difficulty in any patient (with ectopic splenic tissue particularly in the ITP patients) who required reoperation?

Second, in some series, the incidence of conversion to AIDS positive has been distressingly high and increasing over a period of time to about the level of 25%. My concern is whether or not this has been seen in your population and whether this will affect the course of treatment of these patients.

Dr. Robert E. Jones (Closing discussion): Dr. Laws asked several pertinent questions, specifically, what our indications are for staging laparotomy in Hodgkin's Disease. In clinical Stage I and II disease (both A and B), we do perform staging laparotomies. It is only in the Stage III-B patients that we do not operate, and in some patients with clinical Stage III-A disease in which there is massive lymphadenopathy. Also if a person has massive thoracic lymphadenopathy in any stage with the tumor burden greater than one-third of the diameter of the chest, we do not perform a staging laparotomy in these patients.

The question of neutropenia playing a part in our mortality was pertinent. Approximately 30% of the operative deaths were due to sepsis postoperatively. This was primarily in the TTP group, which accounted for 30% of our total mortality.

The postoperative prophylaxis recommendations are that we do not give penicillin to everyone, only to the children who have splenectomy.

Currently we have not operated on the AIDS patients. We do expect that in the near future we probably will. This may be due to the big spleen syndrome.

Dr. Halpern asked a question about hereditary spherocytosis. Our average age was 14 years and our age range was 18 months to 48 years. We do recommend that a child greater than 3 years old have a splenectomy only for severe refractory hemolytic anemia, not in the mild to moderate hemolytic group; and in TTP, we do not have enough experience for treatment recommendations for splenectomy at present.

Dr. Greenfield asked about any difficulty with accessory spleens. We had a total incidence of approximately 12.3% accessory spleens with 30% occurring in the ITP group. We have no documented cases of relapse due to accessory splenic tissue.

In the October 1987 issue Annals of Surgery, from Duke University there is a recent report in which they used Indium labelled platelets and intraoperative hand-held isotope probes to localize accessory splenic tissue with excellent results.

As stated previously, Dr. Greenfield, we have currently not operated on the AIDS patients, but possibly in the near future we will, due to our referral pattern.

The Surgical Management of Esophageal Stricture in Children

A Century of Progress

H. BIEMANN OTHERSEN, JR, M.D., EDWARD F. PARKER, M.D., and C. D. SMITH, M.D.

Early in this century all procedures performed on the esophagus were accomplished through its lumen. Ingestion of caustics was common and resulted in dense strictures for which complicated and ingenious methods of dilation were advised. Because obstructions usually recurred, by-pass operations were devised with conduits of skin or segments of the gastrointestinal tract. Now, in contrast, when burns occur, intensive steroid therapy usually prevents all but localized areas of stricture. These areas, if short, can be treated with hydrostatic balloon dilation under fluoroscopic control. If longer or resistant to dilation, these strictures can be managed by incision and insertion of a colic patch with excellent long-term results. To a previous series of children who have had esophageal patch with a vascularized segment of colon, now added is an experience with a free segment of small intestine with vascular anastomosis to an artery and vein in the neck and another case of a free patch of pericardium to the esophageal stricture.

From the Divisions of Pediatric Surgery and Cardiothoracic Surgery, Medical University of South Carolina, Charleston, South Carolina

IN THE PAST 100 years, advances in medicine usually have occurred as a consequence of refinements in technique rather than as the result of new ideas and concepts. On the occasion of the 100th anniversary of the Southern Surgical Association, we felt that progress made in the management of esophageal strictures in children should be reviewed in order to define and refine current therapeutic regimens. Since an extensive review of the medical literature in English and in German disclosed no reports of experience with the colic patch in children, with the exception of the original description by Hecker and Hollmann,[1] it appears that our series of patients is unique and should be updated and assessed in light of historical review.

Within the past century, rapid progress has been made in the prevention and nonoperative therapy of esophageal strictures in children. In contrast, appendicitis, which was described by Reginald Fitz almost 100 years ago,[2] has experienced no advance in prevention, diagnosis, or therapy. Despite the most advanced computerized radiographic, magnetic, and nuclear imaging studies, the diagnosis of appendicitis is still based on clinical history and physical examination. Furthermore, the surgical therapy of appendicitis basically has remained unchanged for the past 100 years. This is not so for the esophagus!

This article presents the major milestones in the development of surgical therapy of esophageal strictures in children. Included are preventive measures as well as nonoperative therapy. The indications for and techniques of colic patch esophagoplasty have been reviewed and our series updated.[3]

The concept of incision of an esophageal stricture and insertion of a patch was orginally reported for the cervical and also the terminal esophagus. Not until Hecker and Hollmann's work was the application of this concept possible to the thoracic esophagus. We have extended their work and demonstrated the effectiveness of this technique in a series of children.

History

"What's Past is Prologue"
William Shakespeare
The Tempest (II.i.253)

Early medical writings concerned with the gullet, or esophagus, described various ingenious techniques and instruments for the extraction of foreign bodies. Their primary interest was relief of esophageal obstruction that could be caused by carcinoma or benign scars. Most strictures then were approached by internal esophagotomies and repeated dilations. In his book, *Thoracic Surgery before the 20th Century,* Hochberg describes an operation by Llobet that was performed in 1900.[4] Llobet

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Presented at the 100th Anniversary Meeting of The Southern Surgical Association, Hot Springs, Virginia, December 6–9, 1987.

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proached the esophagus extrapleurally through the osterior mediastinum.[5] He then performed longitu-inal incisions through the strictures of the lower esoph-gus. The wounds in the esophagus were left open after a oft rubber tube had been passed into the stomach ansnasally. Not surprisingly, the patient died on the th postoperative day.

Surgeons in the late 19th century operated on the ervical esophagus and avoided the pleural cavity before he development of positive pressure anesthesia. In 894, Bircher described an operation to circumvent an bstructed esophagus by the formation of a tube fabri-ated from the skin of the anterior surface of the thorax.[6] lthough the procedures were well planned, both of his atients died before the final stages could be completed. n 1920, Saint published a thorough treatise on esopha-eal repairs summarizing the knowledge at that time.[7] In complete and detailed review published in 1934 and ntitled, "Anterothoracic Oesophagoplasty for Imper-meable Stricture of the Oesophagus," Ochsner and Owens summarized the procedures that had been used p to that time.[8] They collected 240 cases from the world literature and added one of their own. There is no ecorded case of a completed esophagoplasty having een performed in the United States before this report. igure 1 shows a diagram from their paper that illus-rates the various techniques of esophagoplasty. Proce-dures used on both children and adults were: dermato-sophagoplasty (skin tube from the proximal esophagus o the stomach); jejunoesophagoplasty (jejunum from sophagus to stomach); jejunodermatoesophagoplasty jejunum from stomach to skin of chest wall and skin ube to neck); coloesophagoplasty (colon from stomach o neck); salpingogastroesophagoplasty (gastric tube to roximal esophagus); gastroesophagoplasty (entire tomach to the cervical esophagus). From their review nd personal experience derived from one case, the au-hors believed that anterothoracic esophagoplasty hould be used only in cases of absolutely impermeable enign stricture. Although they believed that the results with coloesophagoplasty were equally as good as those with jejunodermatoesophagoplasty, they preferred the atter technique. (Figs. 2–4)

An esophageal patch technique, which consists of in-cision of the lower esophageal stricture and coverage of the resulting defect with the serosal surface of the fundus of the stomach, was described by Thal and co-workers in 1965.[9] Thomas et al. added a skin graft to the serosal surface of the fundus before its application to the esoph-ageal defect and also advised fundoplication.[10] This technique has not received universal favor among sur-geons. In 1979, Hugh and his associates described the use of a vascularized antral patch with the pedicle based on the left gastroepiploic vessels.[11] The mucosa of the antrum was applied to the lumen of the esophagus and a concomitant fundoplication was performed. This technique was used only for esophageal strictures.

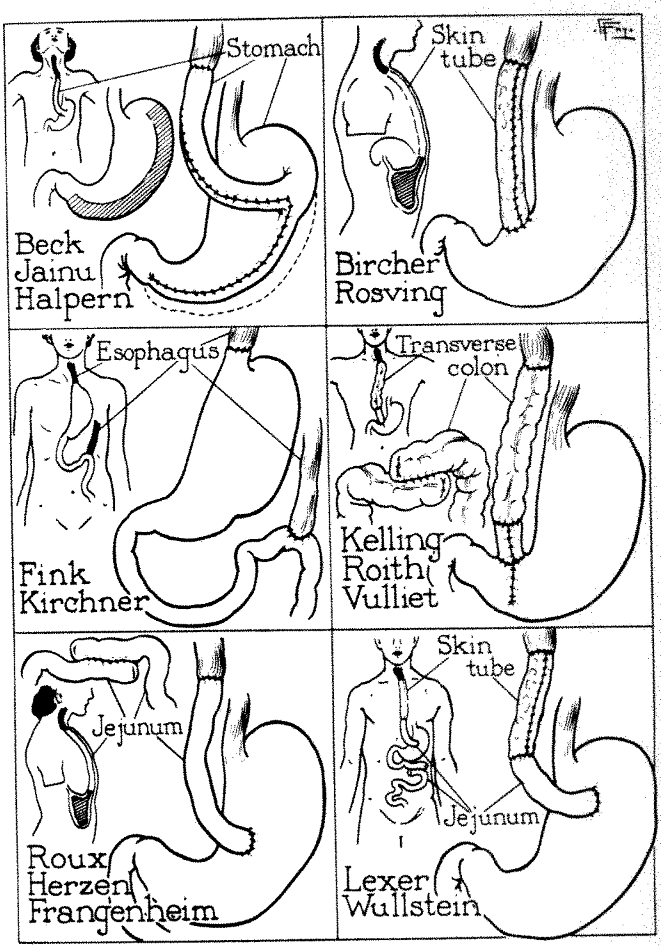


FIG. 1. Diagrams of the early extrathoracic procedures designed to bypass esophageal obstruction (from Oschner and Owens[8]).

No technique of vascularized patches inserted into the thoracic esophagus could be found before the publica-tion by Hecker and Hollmann in 1975.[1] They per-

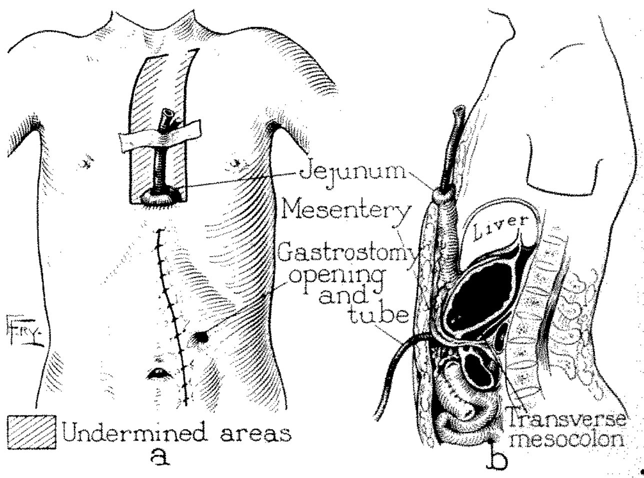


FIG. 2. First stage of bypass operation using a jejunal tube to the stomach and then attached to a skin tube to the proximal esophagus (from Oschner and Owens[8]).

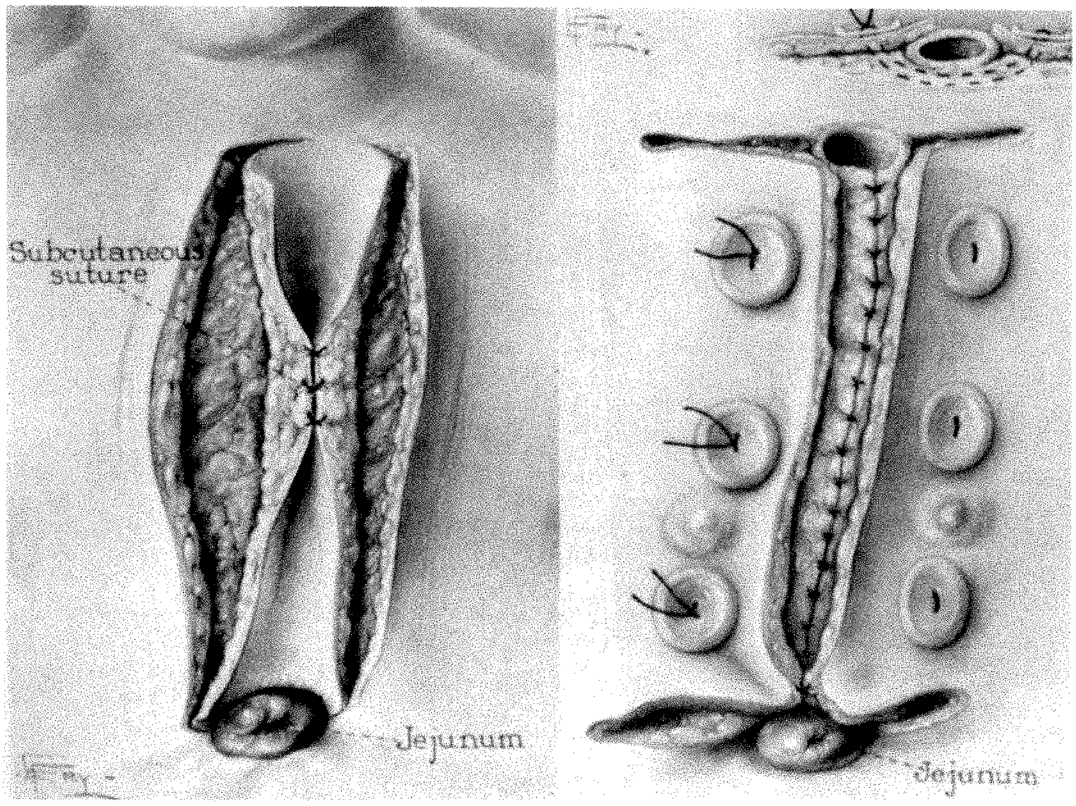


FIG. 3. The skin tube is fashioned to bridge the gap between the jejunal loop and the proximal esophagus (from Oschner and Owens[8]).

formed initial experiments in dogs and reported two patients who were treated with this technique. There has been no subsequent publication of follow-up of those patients or the addition of any new ones. Dr. Antonio Gentil Martins of Lisbon indicated that he has presented this concept at a meeting but the report was not published. In 1985, we reported a 10-year experience with the use of the vascularized colic patch in the management of esophageal strictures in children.[3] Before that time, we initially had used gastric tubes but subsequently preferred the left colon brought up in an antiperistaltic manner and placed in the posterior mediastinum (Figs. 5A–C). Long-term follow-up of children with esophageal replacement revealed good initial function but eventual redundancy and stagnation in the interposed colon often associated with marked growth retardation.[12] We have been satisfied with the long-term results of the colic patch.

Prevention

Most esophageal burns are caused by the ingestion of caustic substances, lye in particular. Extensive educational programs have been launched in an effort to convince families not to use these corrosive substances and, if they must, not to store them in containers that ordinarily hold nondangerous substances. In the event of a serious esophageal burn, experimental evidence has shown that transmural burns are necessary for strictures. Prompt treatment with high doses of steroids and antibiotics or with intraluminal stents has prevented the development of extensive scarring and strictures throughout the entire esophagus.[13] Strictures may occur despite intensive steroid therapy, but they often tend to be more localized and amenable to treatment once the steroid therapy has been initiated. In the repair of esophageal atresia, the use of absorbable sutures of polyglycolic acid and the performance of the anastomosis in a single full-thickness layer have reduced the incidence of postoperative anastomotic stricture. Foreign bodies are now easily extracted with rigid or flexible endoscopes, and smooth objects such as coins can be retrieved without anesthesia by use of a Foley catheter under fluoroscopic control. Disc batteries, lodged in the esophagus, should be removed by esophagostomy before they produce necrosis and eventual stricture by leaking caustic chemicals and by galvanic action.[14]

Nonoperative Therapy

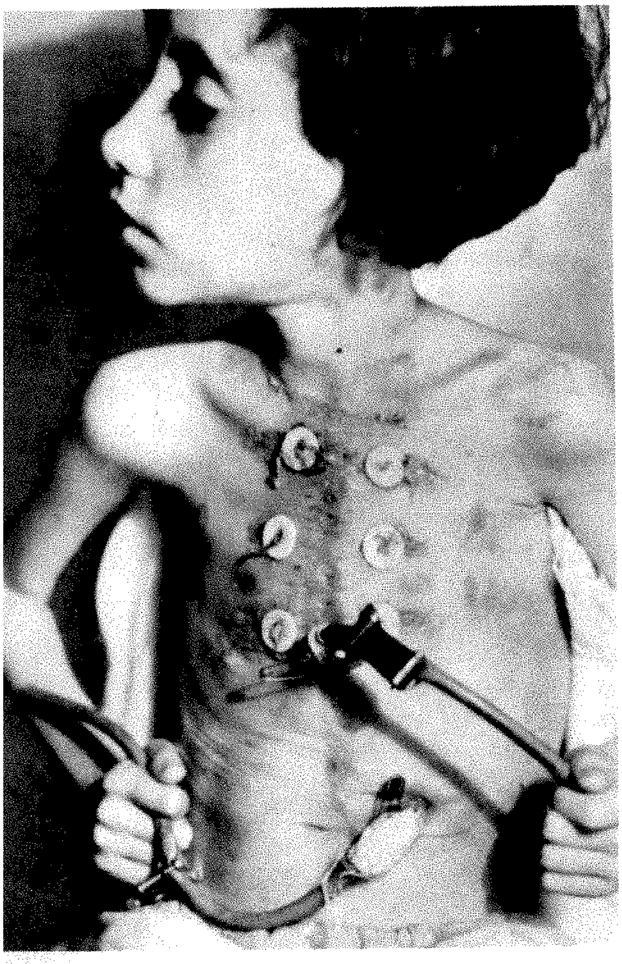
After the administration of high-dosage steriods or the insertion of an intraluminal stent has allowed healing of the acute injury, transmural necrosis may lead to strictures that are relatively localized. Anastomotic strictures are generally limited in their extent and respond well to balloon esophagoplasty early in their development before dense scarring occurs. Balloon esophagoplasty is accomplished through the use of angioplasty balloons, which can be located precisely in the stricture and dilated under fluoroscopic control. The inflation is guided manometric monitoring to confirm that the balloon s reached its proper diameter. This type of dilation ould prove much more effective than either antegrade retrograde bouginage due to the fact that the balloons ıply a radially directed force that stretches the stricture thout the shearing component, which may produce ucosal avulsion.

Surgical Therapy

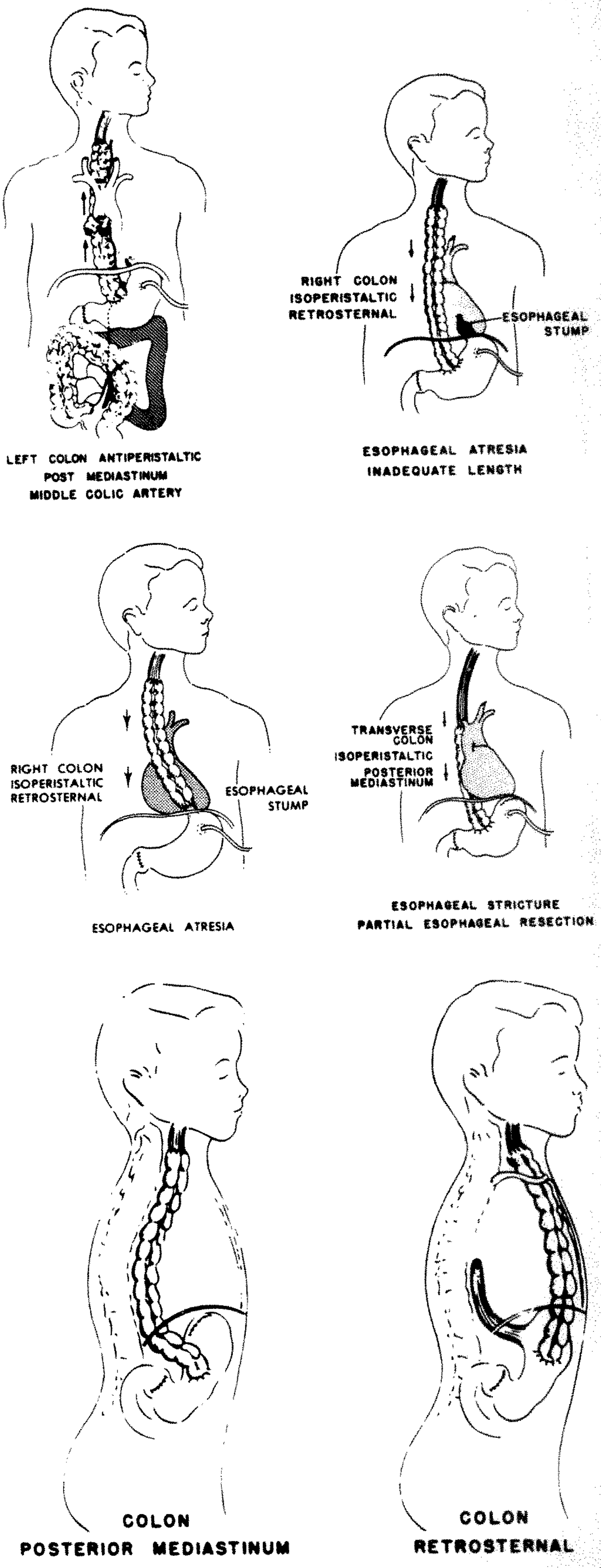
Many surgical techniques developed for esophageal placement are still in use and Table 1 lists the advanges and disadvantages of the various esophageal reacements.

Colic Patch

Since this procedure was described and reported in)75, it has been used by the Pediatric Surgical Service the Medical University Hospital for the past 12 years. he technique is the same as described by Drs. Hecker ıd Hollmann with a few modifications.[1] We have used ɔth the extrapleural and transpleural approaches and



ɪG. 4. A child in whom a jejunal and skin tube has been constructed from Oschner and Owens[8]).



FIGS. 5A–C. Diagrams of various varieties of colic interposition. All of these, whether iso- or antiperistaltic and whether in the post mediastinum or substernally, function as conduits and empty by gravity.

TABLE 1. *Intrathoracic Esophageal Substitutes*

Technique	Advantages	Disadvantages
Small intestines	Large amount of intestine available	Blood supply lacks a marginal artery; difficult to obtain a straight conduit with good blood supply
Gastric tube	Stapling devices have simplified construction of the tube	Long suture line; may not be able to reach high in the neck; difficult to place in the posterior mediastinum
Colon	Acts as a conduit when placed either anti- or isoperistaltically; good blood supply with marginal artery and can reach high in the neck; can be placed in the posterior mediastinum in the esophageal bed	Long-term growth retardation; late redundancy and stasis; late strictures at the cologastric anastomosis
Entire stomach	Readily available and easy to mobilize	Blood supply may not allow it to reach high in the neck; large bulk may cause space problems when brought up intrathoracically
Colic patch	Can be tailored to the individual esophageal defect; good blood supply to reach high in the neck; does not require esophageal resection; esophageal continuity intact	Long suture line; cannot be used when entire esophagus is densely scarred; the scarred esophagus is left in place
Free patch of intestines	Only short portion of gut used—no useful intestine discarded; can be tailored to the individual area	Requires microsurgical anastomosis with threat of thrombosis and gangrene
Free or pedicled patch of pericardium	Readily available material and does not require vascular pedicle	Contracts and stricture may recur

believe that each is adequate. The segment of colon is based on the middle colic or the left colic artery. Careful measurements determine the length needed. The esophageal stricture is incised longitudinally until normal esophagus is reached at each end of the stenosis. A template of the patch size required is then made. The colic segment is opened on its antimesenteric border. The patch is fashioned while still in the abdomen. If the segment of colon is first brought into the chest and then trimmed, its location deep in the thoracic cavity makes control of hemorrhage more difficult. The colic segment is more accessible in the abdomen. When the patch has been fashioned, it is passed behind the stomach and through the esophageal hiatus into the chest. The patch should fit without redundancy and is sewed into place with polyglycolic acid sutures—either continuous or interrupted (Fig. 6). A 10-year report of results was published in 1985 with excellent long-term results in six patients and good results in three patients.[3] There were no major complications, but in three patients there was a tendency of the patch to bulge, producing a pseudodiverticulum. However, the functional results were good. When the patch was perfectly tailored to the defect, no bulging or redundancy was found. Endoscopic evaluation after patching showed good epithelial covering of the area of previous stricture with improved pliability of the esophageal wall. The patch is easily identified by the mucus adherent to it and by a slightly darker color of the mucosa.

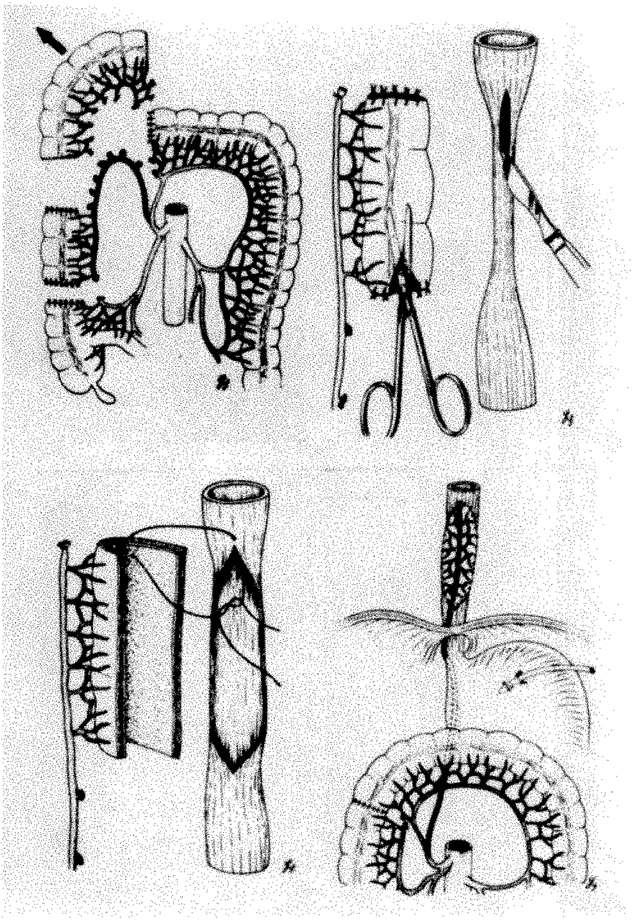


FIG. 6. Four steps in construction and application of a colic patch (from Hecker and Hollmann[1]).

Subsequent to our report,[3] we have used a free patch of small intestine anastomosed by microsurgical techniques to vessels in the neck. This patch was interposed into the cervical esophagus after a dense stricture resulted from caustic ingestion. A previous gastric tube interposition had also been used and a cervical leak had occurred, which added to the scarring. The free patch worked well with the exception of the development of an esophagocutaneous fistula at its lower margin where it was sutured into the esophageal defect. At that point on the patch, a single layer of chromic catgut was used; a second layer of polyglycolic sutures was not placed for fear of compression of the blood supply to the patch. In retrospect, a second layer of sutures should have been placed carefully or the single layer should have been polyglycolic acid sutures. In an additional case, a young boy had ingested lye and initial esophagoscopy showed an extensive burn. High-dose steriods (4–6 mg/kg/day of prednisone) were given and, eventually, a localized stricture (2 cm) remained as the only residual problem. The stricture was located in the distal esophagus but the remainder of the esophagus healed well without stenosis. Since the stricture was so short, it was believed that a free patch might allow the stenosis to be incised without the necessity of constructing a pedicled flap. The stenotic segment was therefore incised and the esophageal defect closed with a free patch of pericardium. Initial results were good and the patient was able to swallow without difficulty, but gradually, over 6–12 months, the stricture in that area recurred as the patch contracted. He has had balloon esophagoplasty but the stricture has recurred three times. If the stricture again returns, a pedicled colic patch will probably be required.

The advantages and disadvantages of the colic patch are listed in Table 2.

TABLE 2. *Colic Patch Esophagoplasty*

Advantages	
	Retains continuity of esophagus
	Less injury to vagus nerves
	Permits re-epithelialization and scar regression in surrounding esophagus
	Amenable to anastomosis of vascular supply to local vessels
Disadvantages	
	May form pseudodiverticulum if redundant
	Long intrathoracic suture line
	Difficult to carry anastomosis into the neck

Discussion

The colic patch currently offers advantages that outweigh any disadvantages. It is easily constructed and, with a good marginal artery, can be carried high into the chest. The only problem has been that a considerable amount of colon must be discarded to obtain adequate length to the pedicle, but the same amount of bowel would be used for a tubular colic interposition.

The current alternative operations are replacement or bypass with stomach, small intestine, or colon. The entire stomach, when brought up to the proximal esophagus, refluxes and occupies a large space in a small chest. The gastric tube also allows reflux of acid secretions and may not easily reach high enough. Small intestine lacks a marginal artery and must be redundant. Swallowing is a slow process when food must traverse an interposed piece of small intestine.

If the scarred colon is bypassed, it may accumulate secretions and eventually perforate or carcinoma may develop in the retained scar. This concern also may be applied to the colon that remains after a colic patch. There have been reports of carcinoma developing years after a chemical burn but the average time from injury to carcinoma is 30–40 years with a frequency of 1.2–2.6%.[15–17] Carcinoma has also been reported in anterothoracic dermatoesophagoplasties. In our patients who have had interposition of a colic patch, the scar in the esophagus has become much more pliable as the tension is relieved after insertion of the patch. Portions of the esophagus, which prior to the patch contain scar epithelium and granulation tissue, eventually become covered with esophageal mucosa. The possibility of carcinoma developing in some of our patients exists, but the risk is minimal.

Summary

In reviewing the progress of treatment of esophageal strictures in children over the past 100 years, there has been considerable improvement in our therapeutic regimens. The surgical treatment of strictures has been greatly facilitated by the use of the colic patch in which the interposed segment can be tailored to match the gaping defect after a longitudinal esophagotomy through the stricture. The esophagus is not resected from its bed and its nerve supply is not interrupted. There is admittedly no substitute for the damaged and scarred esophagus, but of the available conduits, the colic patch has been most satisfactory in our hands. We believe it will become the preferred method of treatment of esophageal strictures.

Acknowledgments

The authors express their deep appreciation to Megan Othersen for her dedicated editorial assistance and to Barbara Tamsberg for her expert typing of the manuscript.

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DISCUSSION

DR. J. ALEX HALLER (Baltimore, Maryland): It is a pleasure to hear this excellent presentation and to have had the opportunity of reviewing Dr. Othersen's manuscript. While he has, in his manuscript, focused on the need for methods of replacing the injured esophagus, he also very properly emphasizes the importance of preventing the stricture, and I think that may have been an even more important development over the last 100 years than these various operative procedures for the correction of the established stricture.

We have not had the opportunity of using the colon patch in this country that Dr. Othersen himself has described, following the report from Germany; but I would like to ask him about any long-term complications in these children, because my personal worry is that abnormal mucosa in this position might actually represent a site for the development of carcinoma over the 50, 60, or 70 years that lie ahead.

I would like to ask him whether this has been reported at all from the European experience, or whether those children have lived long enough to have developed any such complications.

The other technical question is: How long a segment can the colon patch replace? In the shorter strictures, we have felt it is better to resect and carry out a primary anastomosis, and not to bring up a segment of jejunum or colon. In the last 10 years, using the primary steroid treatment which he has outlined, we have had only one long-term stricture following caustic injuries in children. That was a short stricture, and it was possible to correct it with resection and a primary anastomosis.

I would like to ask one other question, and that has to do with the experience with some of the liquid sodium hydroxide agents that are currently becoming more and more available in the homes. Until recently, I did not think they were a problem in children and young teenagers; but recently I heard the remarkable experience in Winston-Salem of a group of teenagers who found liquid sodium hydroxide in the refrigerator, thought it was wine, rapidly drank it, and all of them had severe esophageal burns, and some also perforated their stomachs.

Dr. Othersen, have you dealt with this sort of problem before, and is this going to be an increasing problem now and for the next 100 years?

DR. MAURICE J. JURKIEWICZ (Atlanta, Georgia): I want to compliment Dr. Othersen on two things, not only his presentation, but also that he is now from the Division of Plastic Surgery at the Medical University of South Carolina, so the program states. I don't know how that happened.

I should like to make a comment on your own experience and ask two questions. The questions that I have are similar to that of Alex Haller. What is the long-term follow-up on such patients? Is there a possibility of cancer arising in that damaged yet recovered segment?

(Slide) These data were put together by John Coleman in our institution. They relate to the experience we have had with jejunum autografts transplanted into the neck and other areas. These data are limited to transplants of jejunum done in the neck. We have had experience with patch grafts in the 13 patients, six of which were in patients with cancer and seven with benign conditions. We use either a cylindrical tube to replace the entire segment filleted as a patch.

(Slide) The stricture was limited to the cervical esophagus. As you can see, she had a ribbon of apparently normal mucosa in the posterior wall of the esophagus. A patch graft was used (Slide), revascularized in the neck.

We reported her and other patients to this organization in 1983. She continues to do well.

All of the patients with benign conditions in whom the cervical esophagus has been replaced with jejunum have done very well, indeed.

May I ask whether there has been a problem with vascular thrombosis, particularly on the venous side? There must be technical problems associated with mobilizing such long segments.

DR. EDWARD F. PARKER (Closing discussion): I want to thank the discussants first.

Dr. Haller first mentioned the question of carcinoma in the transplanted colic patch. We have had no experience with it. I doubt if sufficient time has elapsed to see whether or not carcinoma would develop, and we have nothing more to say.

How long a segment has been patched? In this series, it has been up to 8 and 10 cm in the thoracic esophagus.

I can't equal Dr. Campbell's histrionics or illustrations of liquid caustics, but in connection with the liquids, we would only have to say that we hope that legislation might control some of it, including some of the alcoholic beverages we are invited to drink at times.

On the long-term follow-up, there hasn't been enough time to see whether or not carcinoma would develop, or whether or not there is going to be any carcinoma in any residual burn of the esophagus which might not present enough scar to excise at the time of operation. Grossly one leaves no scar.

As far as carcinoma and scar are concerned, at the Medical University of South Carolina hospitals, in over a thousand patients, we have seen very, very few that were associated with scars. In one that I remember in particular, the patient had a scar, but the carcinoma did not arise in the scar, so I don't know the causal relation between scar and carcinoma in our cases.

Now, we might add that surgeons have long had access to the cervical and the abdominal esophagus, but prior to the 1975 publication of Hecker and Holman and a subsequent similar description by Othersen and Smith in 1985, restoration of the ability to swallow usually has been restricted to one of several methods described by Dr. Othersen, and also to the use of transplantation of fascia, either adjacent or distant. Even the fascia lata has been used in the past to fill-in a defect in the esophagus.

Since the advent of the colic patch method used as described, we have had one case in which a free pericardial patch was used. The initial result was satisfactory, but the late, unsatisfactory, and the patient may become a candidate for the colic patch technique of repair if the recurrent stricture does not respond to hydrostatic dilatations.

We have also used a free loop of jejunum, which Dr. Jurkiewicz has illustrated so beautifully in past years, for transplantation to the neck with anastomosis of the artery and vein to corresponding cervical vessels, and a fastening of the patch as described. The result has been extremely good.

As far as the various liquids that cause trouble are concerned (not so much in children, but in adults, especially those suicidal or accidental), we have no idea what they drink because many times they are drunk and they don't know, either. The amount of injury that can be caused is unbelievable. In one adult, the last one we operated on, not only was the esophagus destroyed, the stomach was destroyed also. At the time of gastrectomy, the lumen was literally reduced to a size that would not accommodate anything more than my thumb. We ended by having to do a total esophagogastrectomy and using a colic transplant between the cervical esophagus and the duodenum. Then we had to do secondary operations later, because the proximal end of the colic patch became necrotic, probably due to a pectus recurvatum at the manubrial end. The pressure, I think, caused the necrosis. Finally, we excised the manubrium and used a tubular jejunal graft, again as described by Dr. Jurkiewicz, between the cervial esophagus and the remaining viable colic transplant. The end result has been most satisfactory.

Prior to 1975 and since, we have found in the literature no mention of any direct operation on a stricture of the thoracic esophagus by luminal enhancement by interposition of a loop of colon that has been incised longitudinally on its antimesenteric border. This method allows the colic loop to serve as a patch, its corners trimmed to match the contour of the esophageal defect to close the longitudinal, widely gaping incision with very gratifying results.

Comparison of Percutaneous Endoscopic Gastrostomy with Stamm Gastrostomy

JOHN P. GRANT, M.D.

In a review of 125 percutaneous endoscopic gastrostomies (PEG) and 88 Stamm gastrostomies performed at Duke University Medical Center since 1978, the average operating room time for PEG (50 ± 20 min) was shorter than for Stamm (96 ± 26 min) ($p < 0.0001$). General anesthesia was administered in only 13% of PEG placements compared with 64% of Stamm gastrostomies. The cost of PEG was about $1000 less than for Stamm gastrostomies. The average time after surgery until use of the feeding tube was 1.8 days for PEG compared with 3.4 days for Stamm ($p < 0.0001$). The overall complication rate after PEG was 8.8% (4.0% major) compared with 23.9% for Stamm gastrostomies (10.2% major) ($p < 0.005$). PEG reduces operative time, necessity for general anesthesia, expense of insertion, incidence of complications, and requires less recovery time before use. PEG is the procedure of choice for gastric feeding access.

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EGEBERG IS CREDITED WITH first expressing the concept of a gastrostomy in 1837. Sedillott successfully performed gastrostomies in dogs in 1839 but failed in three attempts in humans in 1846 with all three patients dying. It was not until 1876 that Verneuil performed the first successful gastrostomy in humans. Since then, numerous modifications have been suggested including a serosal tunnel by Witzel in 1891, permanent gastrostomy tubes by Janeway and Beck-Jianu in the early 1900s, and a valved gastric tube by Glassman in 1939. The most successful and most commonly used technique today, however, was proposed by Stamm in 1894 using concentric purse string sutures to invaginate the serosa about a tube passed into the stomach. Although relatively simple to perform, the Stamm gastrostomy has been associated with a significant incidence of complications including wound infections, gastric bleeding, skin erosions with leakage about the tube, pain at the exit site, anesthetic complications, and occasional death. In an extensive review by Mamel, 264 complications were seen in 1438 Stamm gastrostomy placements (18.4%) with 9.8% of major and 8.7% of minor complications.[1] These complications are due in part to the use of general anesthesia, need for a laparotomy in often malnourished patients, and technical difficulties with placement and securing of the purse string sutures. One publication by Smith and Farris in 1961 is notable for its large number and unusually good experience placing 2512 Stamm gastrostomies with only nine complications (0.4%).[2]

In 1980, Gauderer et al. described a technique for endoscopic placement of a feeding gastrostomy tube, which could be performed under local anesthesia and did not require a laparotomy.[3] In a limited but growing experience, a complication rate one third of that of Stamm gastrostomy has been reported, comprised mainly of tube exit site infections and aspiration pneumonias.[1,4,5] This review was undertaken at Duke University Medical Center to compare results of percutaneous endoscopic gastrostomy with Stamm gastrostomy with respect to operative time, use of general anesthesia, incidence of complications, time prior to use after placement, and cost.

Methods

The records of all patients who underwent placement of a feeding gastrostomy by the author from November 1978 through November 1987 were reviewed. Early in the series all patients had a Stamm gastrostomy placed. As experience with percutaneous endoscopic gastrostomy increased, most patients received a percutaneous endoscopic gastrostomy. No randomization was performed. Patients with acute peritonitis, delayed gastric

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emptying, significant esophageal reflux, or cirrhosis with portal hypertension, ascites, or esophageal or gastric varices, were excluded. Prior abdominal surgery was not an exclusion factor unless the surgery had involved a partial or total gastrectomy.

The following standard technique was used for Stamm gastrostomy. A 6–8-cm midline incision was placed and a 22–28 F Silastic Malecot gastrostomy tube inserted high on the anterior gastric wall using 2–3 concentric purse string silk sutures to invaginate the gastric wall about the tube. The tube was brought out a separate stab wound in the left upper quadrant and the stomach was sewn to the abdominal wall at the tube exit site. The midline incision was closed primarily. The tube was connected to straight drainage. When drainage was minimal and bowel sounds were normal, the tube was clamped and bolus gastric feedings begun.

Percutaneous endoscopic gastrostomies were placed using a modification of the technique of Gauderer et al.[3] Patients were given 10 mg of diazepam as a preoperative sedative when necessary and 1 g of cefazolin on call to the operating room. The abdomen was prepared for surgery with povidone-iodine soap, alcohol, and povidone-iodine solution and draped in a sterile fashion. A pediatric gastroscope was introduced into the stomach, carefully observing the esophageal lumen during passage to assure no strictures or other abnormalities. The stomach and pylorus were also examined to rule out the presence of varices or stricture. The stomach was insufflated with air through the gastroscope until it was fully distended. The light of the scope was directed anteriorly and the lights in the operating room dimmed, allowing visualization of the light through the abdominal wall. The presence of a sharp, circular light image assured that there was no intervening bowel or liver between the stomach and the anterior abdominal wall. The point of maximal light transillumination was selected for the gastrostomy site and was usually about one third of the distance along a line from the left costal margin at the midclavicular line to the umbilicus. Care was taken to always place the exit site at least 4 cm from the costal margin to avoid site irritation. If necessary, the site was adjusted so that palpation with a single finger at the site was clearly seen by the endoscopist as an indentation of the anterior stomach wall confirming apposition of the stomach to the abdominal wall. Occasionally in obese patients or patients with scarred abdominal walls as with prior burns, the light did not transilluminate. In all cases, however, palpation resulted in a clear indentation of the stomach wall and the procedure was continued. If neither sign is present, the procedure should be abandoned. The skin at the selected exit site was infiltrated with 1% Xylocaine* and an incision exactly 1.5 times wider than the diameter of the gastrostomy tube was placed. A larger incision is associated with poor healing, skin irritation and, occasionally, tube erosion. A smaller incision drains poorly and leads to cellulitis at the exit site and occasionally a subcutaneous abscess or fasciitis. A 16-gauge Argyle Medicut "R" catheter was introduced through the incision and advanced into the stomach directing the tip toward the endoscope light (Sherwood Medical Industries, St. Louis, MO). A snare was passed through the endoscope and placed over the end of the Medicut catheter. A #1 nylon suture was passed through the catheter and grasped with the snare. The endoscope and suture were then drawn out through the esophagus and mouth. The Medicut catheter was removed from the abdominal wall and the end of the suture exiting from the mouth tied to the end of a 16 F Glasser Percutaneous Endoscopic Gastrostomy Tube (Biosearch Medical Products, Inc., Sommerville, NJ). The gastrostomy tube was marked with a marking pen at 1-cm intervals from its end for a distance of 4 cm (Fig. 1). The suture material and gastrostomy tube were then lubricated with Neosporin ointment™ (Burroughs Wellcome) and the suture withdrawn from the abdominal wall drawing the gastrostomy tube through the mouth, down the esophagus and out the abdominal wall. The tube was withdrawn until the inner disk retainer drew the stomach tightly against the abdominal wall and an appropriate number of markings for the estimated abdominal wall thickness were seen. The use of markings on the gastrostomy tube permitted omission of the second endoscopic procedure initially proposed by Gauderer et al.[3] to assure the tube was tight against the gastric wall. Eliminating the second endoscopic procedure reduces risks of aspiration and esophageal injury. The outer retainer disk was then slid over the gastrostomy tube and secured tightly against the skin to maintain apposition of the stomach to the abdominal wall. The end of the gastrostomy tube was cut to proper length, an adaptor placed, and the tubing connected to straight drainage. Patients were returned to their hospital beds without going to the recovery room. They were given 1 g of cefazolin every 8 hours for two doses. The PEG tube was connected to straight drainage. When drainage was minimal and bowel sounds were normal, the tube was clamped and bolus gastric feedings were begun. At 48 hours the dressing was removed from the catheter site and the outer disk loosened to avoid erosion of the stomach or skin.

Operating room time from patient entry until departure was recorded along with the recovery room charges, material costs, and professional fees. Patients were followed for 96 ± 164 days (PEG) and 237 ± 392 days (Stamm) to determine the time until use for feeding and the incidence of complications. Statistical analysis was by Student's t-test and chi square analysis.

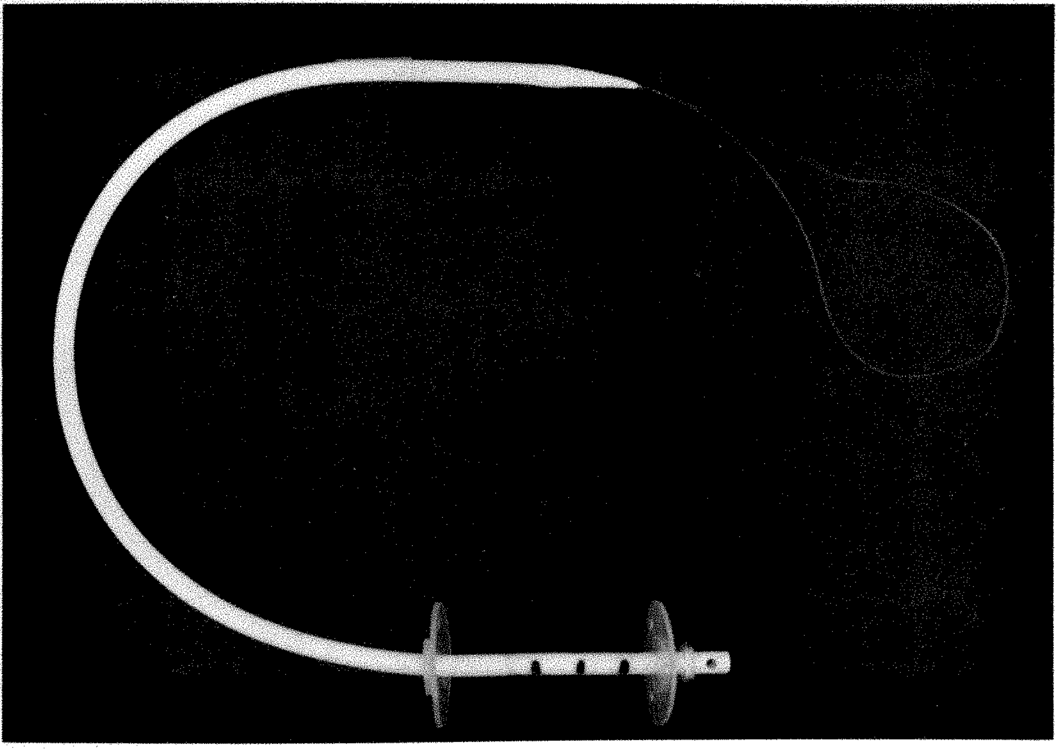

FIG. 1. Percutaneous gastrostomy tube. Note markings at end allowing estimation of distance of stomach from abdominal wall during placement. These markings allow placement by single endoscopy technique.

Results

From July 1981 through November 1987, 125 patients had percutaneous endoscopic gastrostomy tubes placed. In only two cases was the procedure abandoned because endoscopy could not be done. Experience in these patients was compared with 88 Stamm gastrostomies placed from November 1978 through November 1987. Table 1 compares population characteristics. The major indication for gastrostomy placement was altered mental status due to cerebral vascular accidents, primary neurological diseases, and head trauma (64%). Thirty-six per cent had difficulty swallowing due to head and neck tumors or their treatment. The average ASA anesthetic risk for PEG was 3.4 and for Stamm was 3.1 (NS) reflecting multiple other medical problems (Tables 1 and 2). The preference for percutaneously placed gastrostomy tubes later in the series is evident from 1986 and 1987 data that indicated 98 PEG but only 12 Stamm gastrostomies were placed.

The average operating room time required to place a percutaneous endoscopic gastrostomy was 50 ± 20 minutes compared with that for Stamm gastrostomy of 96 ± 26 minutes ($p < 0.0001$). There was a reduction in time for placement of percutaneous endoscopic gastrostomies as experience and expertise increased with an average time of 38 ± 14 minutes for the last 62 tubes placed in 1987. The reduced operating room time for PEG and little need for the recovery room resulted in a savings compared with Stamm gastrostomy of almost $1000 per case. Only 16 percutaneous endoscopic gastrostomies (13%) were done under general anesthesia. Of those, most received general anesthesia either because of other procedures performed simultaneously or for patient comfort in the presence of a tracheostomy. On the other hand, it was elected to perform 57 Stamm gastrostomies (64%) under general anesthesia due to poor abdominal relaxation or patient cooperation. The average time until use of percutaneous endoscopic gastrostomy tubes for enteral feeding, 1.8 ± 0.8 days, was less than that for Stamm gastrostomy tubes, 3.4 ± 2.0 days ($p < 0.0001$). Days to discharge were highly variable (PEG = 55 ± 123 days *vs.* Stamm 26 ± 40 days, $p = 0.117$) and were determined by the patients' primary illness rather than the type of gastrostomy.

Complications after percutaneous endoscopic gastrostomy occurred in 8.8% of patients (Table 3). Two aspiration pneumonias occurred owing to endoscopy, both of which resolved with antibiotics. The one episode of gastric hemorrhage was minor, resolving spontaneously without transfusion. Four of the six episodes of gastrostomy tube exit site infections were minor. Two had significant cellulitis and required antibiotic therapy and drainage. Most exit site infections occurred early in the series and were due to a small skin incision with inadequate drainage about the tube. Only one exit site infection has occurred in the past 98 placements after incisions measuring 1.5 times the diameter of the gastrostomy tube were routinely used and perioperative antibiotics were given. One feeding tube was dislodged by a

TABLE 1. *Patient Characteristics*

	PEG	Stamm	p Value
Number in study	125	88	—
Age ± SD	62 ± 17	58 ± 17	NS
Sex M/F	75/50	52/36	NS
Ave ASA	3.4	3.1	NS
Reason for tube			
Altered mental state	88	43	0.02
Swallow difficulty	37	45	
ASA grade			
Level <2	5	4	
Level 3	71	55	NS
Level 4	44	29	
Level 5	5	0	

confused patient during the first postoperative night. The patient was taken to the operating room immediately and had a Stamm gastrostomy placed. One tube had transient leakage of gastric juice about it. Five tubes were removed when no longer needed without difficulty. No gastrocutaneous fistula developed.

Thirty-one patients had percutaneous endoscopic gastrostomy tubes placed after prior upper (17 patients) and lower abdominal procedures (14 patients) (Table 4). In each case the endoscope light was clearly visualized through the abdominal wall and indentation of the stomach with external pressure at the exit site was clearly visualized. Three morbidly obese patients underwent PEG. Although no light transillumination was seen, palpation was seen to indent the anterior stomach wall. No operative complications were seen in any of these patients.

Complications after placement of Stamm gastrostomies occurred in 23.9% of patients (Table 5). This incidence was significantly higher than for PEG ($p < 0.005$). Seven wound infections occurred requiring partial (3) or complete (4) opening of the wound for debridement and packing. Four instances of tube exit site infections resulted in significant skin erosion and leakage of gastric contents. Intensive local wound care and insertion of a larger tube was required. Leakage of gastric juice at the tube exit site occurred in four additional patients. In one patient it could not be controlled and the gastrostomy tube was removed and replaced with another done by percutaneous endoscopic technique. The old gastrostomy site did not heal and was finally closed surgically. One patient had transient bleeding from the stomach and one patient had the tube withdrawn at postoperative day 3. The tube was successfully replaced under fluoroscopic guidance. Two patients had severe pain at the gastrostomy site and required intermittent use of narcotic analgesics. One patient had gastric outlet obstruction from the tip of the gastrostomy tube lodging in the pylorus.

TABLE 2. *Other Medical Problems Resulting in Increased Anesthetic Risks*

	% Patients	
Problem	PEG	Stamm
Cardiac disease (MI, HTN, arrhythmias)	42	23
Pulmonary disease (pneumonia, failure)	40	38
AODM, renal failure	17	13
Other	8	9

TABLE 3. *Complications of PEG Duke Series of 125 Patients*

2	Aspiration pneumonias from endoscopy
0	Esophageal laceration/perforation
1	Hemorrhage at gastrostomy site (minor)
0	Peritonitis
1	Leakage at gastrostomy site
6	Exit site infections (4 minor)
1	Tube withdrawal from stomach
0	Colonic perforation, gastrocolic fistula
0	Gastrocutaneous fistula after tube is out
11	Overall 8.8% Major 4.0%

Eventual outcome of all patients is depicted in Table 6. No patient died in this series as a complication of placement of the feeding gastrostomy. The high death rate (30.0%) relates to the severity of illness of these patients.

Discussion

Previous reports have documented reduction in operating room time and cost when percutaneous endoscopic gastrostomies are performed compared with standard gastrostomies by laparotomy.[1,6-9] The reduction in total operating room time and little need for the recovery room in this series reduced patient charges by

TABLE 4. *Prior Abdominal Operations in Patients Undergoing Gastrostomy*

	No. of Patients	
Procedure	PEG	Stamm
Upper		
Repair abdominal aortic aneurysm	2	2
Cholecystectomy	7	8
Perforated duodenal ulcer	1	1
Small bowel resection	0	4
Colon resection	0	6
Lysis of adhesions	0	4
Ventriculoperitoneal shunt	5	0
Previous gastrostomy	2	0
Lower		
Appendectomy	7	6
Hysterectomy	6	6
Cesarian section	1	0

TABLE 5. *Complications of Stamm Gastrostomy Duke Series of 88 Patients*

7	Wound infections
4	Exit site infections
1	Hemorrhage at gastrostomy site
4	Leakage at gastrostomy site
1	Tube withdrawal from stomach
2	Pain at tube exit site
1	Pyloric obstruction by tube
1	Gastrocutaneous fistula after tube out
21	Overall 23.9% Major 10.2%

about $1000. The actual endoscopic procedure takes only 10–15 minutes with the remainder of the 30–40 minutes required for patient transfer and establishment of monitoring and intravenous access.

Some physicians advocate placement of percutaneous gastrostomy tubes in the endoscopy suite rather than in the operating room. In selected patients this may be appropriate and would further reduce costs. Most of our patients, however, had significant medical illnesses including poor pulmonary toilet, hypertension, and cardiac disease, and it was believed that for optimal safety the operating room environment was required where airway management could be easily performed and cardiac arrhythmias and arterial oxygen saturation monitored and quickly addressed if necessary. In four of our patients, arterial oxygen saturation by pulse oximeter fell below 90% during endoscopy but was easily treated by adjusting the position of the head, oral suctioning, or administering supplemental oxygen. Oxygen desaturation may go unnoticed in an endoscopy suite possibly contributing to pre-existing altered mental status. The reduced surgical trauma of PEG resulted in a significant decrease in postoperative gastrointestinal ileus allowing earlier institution of gastric feeding. Although abdominal distention due to insufflation of air was common, bowel sounds were usually present within 24 hours of PEG placement and the gas passed through quickly. Abdominal x-rays were not routinely done after PEG placement but when done there was no evidence for pneumoperitoneum.

Only two operative complications of PEG were encountered in this study, both aspiration pneumonias. One possible advantage of the single endoscopic method described herein is the avoidance of potential complications associated with passage of the endoscope a second time to confirm proper tension on the gastrostomy tube. Manufacturers of commercially available percutaneous endoscopy tubes have yet to permanently mark their catheters; however, sterile marking pens provide a satisfactory alternative.

TABLE 6. *Eventual Outcome of Patients*

	PEG	Stamm
Tube removed, oral diet	7	16
Died	31	33
Lost to follow-up	51	33
Continued follow-up, tube OK	36	6

A list of potential complications associated with percutaneous gastrostomy placement (Table 3) suggests to this author that the procedure should be performed by surgeons rather than gastrointestinal endoscopists. Most complications require surgical management and would be most quickly recognized and expeditiously handled by the surgeon.

The safety of placing percutaneous endoscopic gastrostomy tubes in the presence of prior abdominal surgery, suggested by Stellato et al.,[10] is supported by this series. As long as the endoscope light clearly transilluminates through the abdominal wall and/or external pressure at the proposed gastrostomy exit site results in clear indentation of the gastric wall as seen through the endoscope, preferably both, it is safe to proceed without fear of passage through either the liver or interposed bowel.

Conclusions

Percutaneous endoscopic gastrostomy reduces operative time, necessity for general anesthesia, expense of gastrostomy placement, incidence of complications, and requires less recovery time before use for enteral feedings. This study supports the use of percutaneous endoscopic gastrostomy as the procedure of choice for gastric feeding access even in patients with prior abdominal surgery. Stamm gastrostomies should be placed when a laparotomy is performed for other reasons or when gastroscopy is not possible or advisable.

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DISCUSSION

DR. NORMAN HALPERN (Birmingham, Alabama): With any new technique or technology we should ask two questions.

Will it perform a new or different task, or will it better perform an old task? In this case there is nothing really new or different about creating a tube gastrostomy. On the other hand, I am personally convinced that this is a totally superior method for getting the job done.

My experience with 63 patients at UAB is similar to Dr. Grant's larger, carefully reviewed series. I appreciated having a copy of his manuscript and agree with all of his cautions regarding careful assessment of indications and contra-indications, thoughtful attention to the matter of patient safety and monitoring, and to the technical details of the procedure.

An additional application of endoscopic gastrostomy occurred in three of my patients and has been reported by others. That is, for the patient with intra-abdominal carcinomatosis having had repeated episodes of small bowel obstruction and felt to have an unlikely chance of benefit from further surgery. Enteric decompression combined with home parenteral nutrition achieved excellent palliation for periods of 1, 6, and nearly 8 months in these three patients.

I do appreciate the chance to comment and offer support for a procedure that I think really does offer improvement in patient care.

DR. HENRY L. LAWS (Birmingham, Alabama): It appears that Dr. Halpern and I almost have to go as a team.

I think Dr. Grant is to be commended for his critical evaluation of the data on a large number of gastrostomies. From what we heard this morning, this topic is very appropriate, since the first paper given 100 years ago was on gastrostomy.

It is actually disconcerting to me that we are still trying to perfect the operation.

I feel this lowly operation does not receive the attention it deserves. I would differ with Dr. Grant and with my colleague, Dr. Helpern, to some extent in that I think the stapled Janeway gastrostomies are superior to Stamm gastrostomies over the long haul.[1,2]

(Slide) This series was collected by Dr. Fred Swartzendruber, one of our colleagues. What it indicates is that the late complications of Stamm gastrostomies, of which I feel the percutaneous endoscopic gastrostomy is a variant, include late tube malfunction, exit site problems, and so forth, which can be very trying. Neither of these are lined with mucosa. On the other hand, the problems we had with Janeway gastrostomy were very minimal and were minor in every instance.

I would like to ask Dr. Grant how long he followed his patients and how they have been faring over the long haul.

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DR. LEWIS M. FLINT, JR. (Buffalo, New York): I would like to address the use of feeding gastrostomy in a select group of neurologically disabled patients, those who are comatose or obtunded, and to raise the question of whether this operation, regardless of the technique, is indicated and whether it achieves the objectives that we wish it to achieve in the long term.

We recently reviewed 87 comatose or severely obtunded patients in our unit in which feeding gastrostomy was performed for two basic indications, for example, to provide access for nutritional support and, in some cases, to reduce the risk of aspiration pneumonia.

We found that the operation did not, over a two-year follow-up, achieve either objective and that not only was the risk of aspiration pneumonia that existed pregastrostomy not reduced, but about 30% of those patients in whom no aspiration pneumonia could be documented preoperatively developed it postoperatively over the two-year period.

The one-year mortality in our group was 34%, most of this as a result of aspiration pneumonia.

According to our clinical experience, then, gastrostomy did not achieve the objective of reducing the risk of aspiration pneumonia. Neither did it achieve the objective of providing nutritional support, since we could not document nutritional benefit in a single one of our patients in this particular group.

Since we can now acquire and maintain enteral access by the transnasal soft tube technique, using the transpyloric tubes in better than 95% of the patients, I would ask Dr. Grant to comment on the indications, particularly in this select group of patients, and ask him two additional questions. Was the objective of gastrostomy achieved, long-term? And in patients with aspiration pneumonia, does he consider the addition of complementary tracheostomy?

DR. JOHN P. GRANT (Closing discussion): Dr. Halpern has employed percutaneous gastrostomies in a population in which we have little experience: those patients who have distal bowel obstruction and require gastric decompression. I recall several cases where I have placed a Stamm gastrostomy during laparotomy when a diagnosis of carcinomatosis was made to establish proximal decompression. I have been rather disappointed with the clinical benefits, most of the patients dying rather quickly after the operative procedure, and I congratulate Dr. Halpern on his more favorable results.

Dr. Laws, we have very little experience with the Janeway gastrostomy. It is interesting to hear that you feel it is superior to the Stamm gastrostomy.

We have followed our patients on the average for 100 days after percutaneous gastrostomy, and about 200 days after the Stamm gastrostomy. As many patients have gone to distant hospitals or nursing homes, accurate follow-up has been difficult, as you might expect. We know at least 20% have died from their primary disease process. We know another 12% have improved and their feeding tubes have been removed. The remainder have been lost to follow-up after they left the hospital.

Dr. Flint, gastrostomies, I think, are always going to be associated with aspiration pneumonia. It is a complication that is very difficult to avoid in a patient who is not very alert and who is often reclining at the time of feeding, as well as between feedings. It is therefore difficult to distinguish aspiration of tube feedings from aspiration of saliva in patients who have difficulty swallowing. We have had great difficulty sending patients to nursing homes with either a nasojejunal feeding tube or with a feeding jejunostomy. It requires a level of care that they are unprepared (and often unwilling) to assume. In patients who have had repeated bouts of aspiration pneumonia in the hospital, however, I have elected on occasion to place both a gastrostomy for decompression and jejunostomy for feeding, and have been pleased with the results. Another approach that several of our surgeons have taken is to perform both a Stamm gastrostomy and a Nissen fundoplication simultaneously, which, although it may not prevent aspiration of saliva, at least prevents the reflux.

Hemodynamic Dysfunction in Obesity Hypoventilation Syndrome and the Effects of Treatment with Surgically Induced Weight Loss

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and GEORGE W. VETROVEC, M.D.‡

Obesity hypoventilation syndrome (OHS), defined as a $PaO_2 \leq 55$ mmHg and/or $PaCo_2 \geq 47$ mmHg, was found in approximately 8% of morbidly obese patients undergoing gastric surgery for morbid obesity and was frequently associated with clinically significant pulmonary hypertension and cardiac dysfunction. Forty-six morbidly obese patients, 26 with and 20 without OHS, underwent preoperative pulmonary artery catheterization. Although the two groups had similar values for percent ideal body weight, blood pressure, and cardiac index, the OHS patients had significantly higher mean pulmonary artery pressures (PAP), $p < 0.0001$, and pulmonary artery occlusion pressures (PAOP), $p < 0.01$. Eighteen OHS patients were restudied 3–9 months after gastric surgery. PaO_2 increased from 50 ± 10 to 69 ± 14 mmHg, $p < 0.0001$, and $PaCO_2$ decreased from 52 ± 7 to 42 ± 4 mmHg, $p < 0.0001$), after the loss of 42 ± 19% excess weight. These changes were associated with significant decreases in PAP (from 36 ± 14 to 23 ± 7 mmHg, $p < 0.0001$) and PAOP (from 17 ± 7 to 12 ± 6 mmHg, $p < 0.01$). Significant correlations were noted between PAP and PAOP ($r = +0.8$, $p < 0.0001$) and PAP and PaO_2 ($r = -0.6$, $p < 0.0001$). Both left ventricular dysfunction, defined as a PAOP ≥ 18 mmHg, as well as pulmonary artery vasoconstriction, defined as PAEDP > 5 mmHg above PAOP, contributed to pulmonary hypertension in OHS patients. In conclusion, weight loss after gastric surgery for morbid obesity significantly improved arterial blood gases and hemodynamic function in OHS patients.

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In a recent study, 12% of patients who underwent gastric surgery for morbid obesity had respiratory insufficiency of obesity.[1] Of these, one third had obesity hypoventilation syndrome (OHS) alone, one third had obstructive sleep apnea syndrome (SAS) alone, and the remaining third had both OHS and SAS, as in the Pickwickian syndrome.[2] Heart failure has been a prominent feature of patients with OHS.[2-10] In addition, patients with severe OHS are at risk of having a pulmonary embolus, which is often fatal.[11] In previous studies, we have shown that weight reduction in patients with respiratory insufficiency of obesity was associated with significant improvements in the severity of SAS, arterial hypoxemia, hypercarbia, polycythemia, and restricted lung volumes.[1,12] We postulated that hemodynamic dysfunction would be similarly improved. This study used pulmonary artery catheterization to compare hemodynamic function in morbidly obese patients with and without OHS as well as to determine the hemodynamic effects of weight reduction after gastric restrictive surgery in OHS patients.

Materials and Methods

Patient Selection

Patients were accepted for weight reduction surgery if their weight exceeded ideal body weight by more than 100 pounds.[13] Two groups of patients were studied: a control group with no evidence of respiratory compromise and an OHS group with either OHS alone or OHS combined with SAS. Baseline arterial blood gases were obtained in all patients on room air at the time of admission to the hospital. OHS was defined as a $PaO_2 \leq 55$ mmHg and/or a $PaCO_2 \geq 47$ mmHg. Patients with a history suggestive of SAS (*i.e.*, severe daytime somnolence, profound snoring, headache upon awakening,

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restless sleep, or frequent nocturnal awakening) underwent preadmission sleep polysomnography. SAS was diagnosed if multiple apneic or hypopneic episodes were present. Morbidly obese patients who had no evidence of cardiopulmonary disease, systemic hypertension, or diabetes mellitus were asked to enter the control arm of the study. For each patient, per cent ideal body weight (%IBW) was calculated as the ratio of preoperative weight divided by ideal body weight. The study was approved by the Committee on the Conduct of Human Investigation and the Clinical Research Center at the Medical College of Virginia, Virginia Commonwealth University.

Cardiopulmonary Evaluation

Control patients underwent pulmonary artery catheterization in the cardiac catheterization laboratory using flow-directed, thermistor-tipped balloon catheters and fluoroscopic guidance. OHS patients underwent preoperative pulmonary artery catheterization in the Surgical Intensive Care Unit without fluoroscopic guidance. Three to nine months after gastric surgery, 18 OHS patients underwent repeat pulmonary artery catheterization in the Clinical Research Center.

Pressure transducers were zeroed and balanced at the midaxillary line. The pulmonary artery catheters were advanced with the balloon inflated until an "occlusion" tracing was observed. Balloon deflation revealed a pulmonary artery pressure tracing. All pressures were measured directly from the oscilloscope at the end of expiration. The pressure measured with the balloon inflated and the appropriate tracing on the oscilloscope was called the pulmonary artery occlusion pressure (PAOP). The central venous pressure (CVP) was measured from the superior vena caval port of the pulmonary artery catheter. Mean pulmonary artery pressure (PAP) was calculated by determining one third of the difference between the pulmonary artery end-diastolic pressure (PAEDP) and the pulmonary artery systolic pressure and adding this value to the PAEDP. The mean systemic arterial pressure (SAP) was calculated with the same formula from the systolic and diastolic systemic pressures measured with an extra large blood pressure cuff.

Pulmonary hypertension was defined as a PAP $\geq$ 20 mmHg. Pulmonary hypertension was considered to be secondary to left ventricular dysfunction when the PAOP was $\geq$ 18 mmHg and due to pulmonary artery vasoconstriction when the PAEDP exceeded PAOP by $>$ 5 mmHg, regardless of the latter's value. Thermodilution cardiac output was calculated with a Gould-Statham cardiac output computer (model #SP 1453, Gould Inc., Oxmore, CA 93430). Cardiac index (CI) was calculated by dividing cardiac output by body surface area using a standard nomogram. Pulmonary vascular resistance index (PVRI) was calculated by the formula: $[(\mathrm{PAP} - \mathrm{CVP}) \div \mathrm{CI}] \times 79$ and systemic vascular resistance index (SVRI) by the formula: $[(\mathrm{SAP} - \mathrm{PAOP}) \div \mathrm{CI}] \times 79$.

Surgical Procedures, Pre- and Postoperative Management

Over the course of the study (January 1979 through January 1987), a number of different weight reduction procedures were tried. Several of these procedures are now known to be ineffective,[14] including the single-row of staples, unreinforced central stoma, horizontal gastroplasty,[15] and the Gomez gastroplasty.[16] Since June 1982, we have used only vertical banded gastroplasty[17] or Roux-en-Y gastric bypass.[18,19] Patients who failed one of the gastroplasty procedures were offered conversion to gastric bypass, which we have found to provide significantly greater weight loss, especially for patients addicted to sweets.[20] This report will focus on pulmonary artery catheterization data, as the effect of the different procedures on weight reduction[14,20] and pulmonary function[1,12] have been evaluated in previous publications.

Initially, patients with severe SAS or apnea-induced cardiac arrhythmias underwent tracheostomy at the time of gastric surgery. Since 1985, an attempt has been made to treat all SAS patients with nocturnal nasal continuous positive airway pressure (CPAP).[21] Tracheostomy was only performed if the patient could not tolerate nasal CPAP.

Intermittent sequential venous compression boots were used in all patients during surgery and until fully ambulatory to reduce the incidence of thrombophlebitis and pulmonary embolism.[22] After operation, patients were nursed in the reverse Trendelenburg position to maximize pulmonary function.[23] Increased venous stasis from this position made the use of intermittent venous compression boots even more important. In patients with severe pulmonary hypertension (PAP $\geq$ 40 mmHg), a Greenfield® vena caval filter (7 patients) or a Miles® vena caval serrated clip (1 patient) was inserted because of the increased risk of a fatal pulmonary embolism in patients with respiratory insufficiency of obesity[12] as well as the documented danger of fatal pulmonary embolism in patients with primary pulmonary hypertension.[24]

Anesthetic induction was performed with sodium pentothal following muscle paralysis with succinyl choline. At least two anesthesia personnel were present. One was responsible for elevating the jaw, hyperextending the neck, and assuring a tight fit of the ventilation mask over the mouth and nose after insertion of an oral airway. The second person manually compressed the ventilation reservoir bag with both hands because these patients have very low respiratory system compliance. After ventilation with 100% oxygen for several minutes, intubation was attempted. If difficulties were encountered, these steps were repeated until the patient was sucessfully intubated. A radial arterial line was inserted for systemic pressure monitoring and periodic arterial blood gas analysis. A digital pulse oximeter was used to monitor the adequacy of arterial oxygenation from moment to moment.

All control patients were extubated in the recovery room and none required intensive care unit management after surgery. OHS patients were ventilated with a volume ventilator, 1500 cc tidal volume, 5 cm H_2O positive end-expiratory pressure, an F_IO_2 to maintain the PaO_2 above 60 mmHg, and a respiratory rate to maintain the $PaCO_2$ at 40 mmHg. The patients were extubated when they were able to generate −40 cm H_2O inspiratory pressure, 1500 cc vital capacity, and blood gases had returned to preoperative values with a T-piece and room air.

Data Analysis

Data are presented as the mean ± SD. Statistical analyses were performed using Student's t-test for paired or unpaired values, as appropriate. Equal variance was assumed for the latter. P values < 0.01 were considered significant. Pearson correlation coefficients were calculated for preoperative data to evaluate significant correlations. Even though statistically significant, correlations were not considered clinically relevant unless the correlation coefficient (±) was >0.6.

Results

Preoperative Data

Forty-six patients were studied: 20 control and 26 OHS. Of the patients with OHS, nine had OHS alone and 17 had both OHS and SAS. The OHS and control groups had similar preoperative %IBW (Table 1). The OHS group was significantly older, had a greater percentage of men, and had a significantly greater number of patients with an underlying pulmonary disease usually secondary to excessive smoking. The mean preoperative hemoglobin level in the OHS patients was 14.9 ± 2.6 g/dl. Twelve of the 26 OHS patients had a hemoglobin level greater than 16.0 g/dl. Two OHS patients had hemoglobin levels greater than 18 g/dl. Two female OHS patients with dysfunctional uterine bleeding had hemoglobin values less than 11 g/dl and one OHS patient with a Duke's A carcinoma of the cecum had a hemoglobin level of 7.3 g/dl. This patient underwent combined right colectomy and gastric bypass without postoperative complications. None of the control patients had a hemoglobin level greater than 14.4 g/dl.

TABLE 1. *Demographics*

	% IBW	Age (years)	% Men	% Black	% Additional Pulmonary Problem†
Control	229 ± 47	36 ± 9	15	60	10
OHS	225 ± 46	44 ± 11*	54	54	81*

* $p < 0.01$.

† Smoked ≥ 1 pack cigarettes/day except two OHS patients who had asthma.

As expected, the PaO_2 in the OHS group was lower (54 ± 10 *vs.* 84 ± 12 mmHg, $p < 0.001$) and the $PaCO_2$ higher (51 ± 6 *vs.* 39 ± 3 mmHg, $p < 0.001$) than the control group. The SAPs of the two groups were comparable: 101 ± 13 mmHg for control and 100 ± 13 mmHg for OHS. However, the PAP and PAOP were significantly greater in the OHS group (Fig. 1). Seven of 20 control patients had PAP ≥ 20 mmHg; however, none had a PAP above 30 mmHg. No control patients had a PAOP ≥ 18 mmHg. Of the 26 OHS patients, 23 had a PAP ≥ 20 mmHg and in eight it was ≥40 mmHg. Fourteen of the 23 OHS patients with pulmonary hypertension had left ventricular dysfunction, defined as PAOP ≥ 18 mmHg (Fig. 2). Two patients had a PAOP ≥ 30 mmHg and in one, the PAOP was 40 mmHg. The PAEDP was >5 mmHg above the PAOP in 15 of the 23 patients with pulmonary hypertension, implying significant pulmonary artery vasoconstriction (Fig. 2). Six patients had both a PAOP ≥ 18 mmHg and PAEDP 5 mmHg greater than their PAOP (Fig. 2).

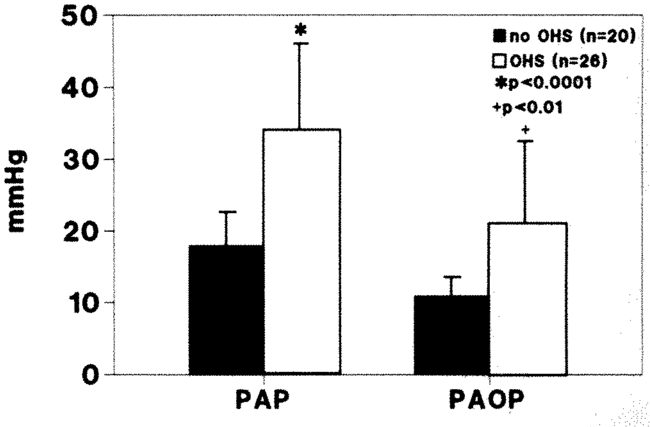

FIG. 1. Significantly higher mean pulmonary artery pressure (PAP) and mean pulmonary artery occlusion pressure (PAOP) in morbidly obese patients with, than in morbidly obese controls without, obesity hypoventilation syndrome (OHS).

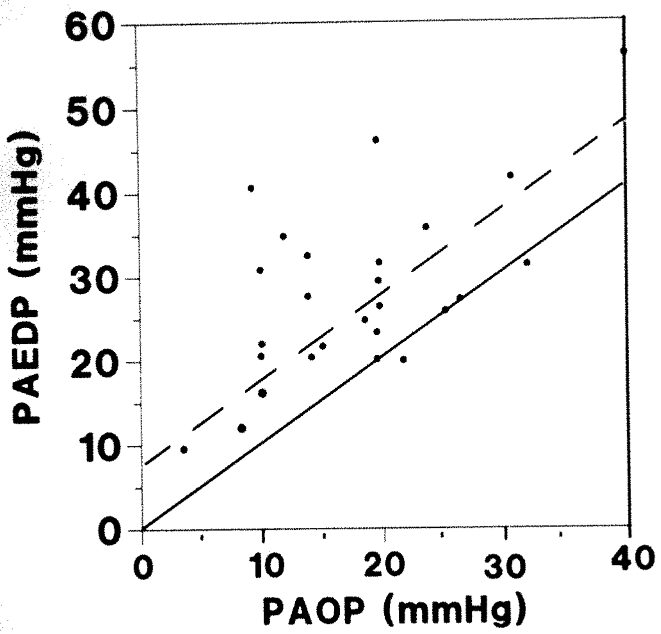

FIG. 2. Comparison of pulmonary artery and diastolic pressure (PAEDP) and pulmonary artery occlusion pressure (PAOP) in obesity hypoventilation syndrome (OHS). Solid line for PAEDP = PAOP. Dashed line for PAEDP 5 mmHg > PAOP.

The preoperative cardiac index was not significantly different between the control and OHS patients, 3.2 ± 0.6 *versus* 3.5 ± 0.6 L/min/m^2, respectively. The systemic vascular resistance index was also not significantly different between the control and OHS patients, 891 ± 183 *versus* 767 ± 223 dynes/cm^{-5}/m^2, respectively. As expected, the pulmonary vascular resistance index was significantly ($p < 0.01$) greater in the OHS group (258 ± 137 dynes/cm^{-5}/m^2) than the control group (147 ± 63 dynes/cm^{-5}/m^2).

The PaO_2 was inversely correlated ($p < 0.0001$) with the PAP, but the correlation coefficient ($r = -0.6$, $r^2 = 0.4$) was not as high as the correlation ($p < 0.0001$) between the PaO_2 and the PAOP ($r = -0.8$, $r^2 = 0.6$). There was no correlation between preoperative hemoglobin and PAP, PAOP, or PaO_2 in the OHS patients.

Cardiopulmonary Effects of Weight Loss in the OHS Patients

Eighteen of the 26 OHS patients underwent repeat pulmonary artery catheterization 3–9 months after gastric surgery for morbid obesity. With regards to the eight patients who were not restudied, four refused, one was lost to follow-up, two had normal preoperative studies, and one patient died suddenly 5 weeks after surgery. This 27-year-old black woman weighed 472 lbs (255 %IBW). Her preoperative PaO_2 and $PaCO_2$ were 50 and 48 mmHg, respectively. Her PAP was 50 mmHg and PAOP 30 mmHg. Multifocal premature ventricular contractions were noted before and after surgery and were treated with quinidine. At autopsy, microscopic examination of her lung tissue revealed normal pulmonary arterial vessels without medial muscular hypertrophy or intimal thickening (Fig. 3). The cause of death was presumed to be from ventricular arrhythmia.

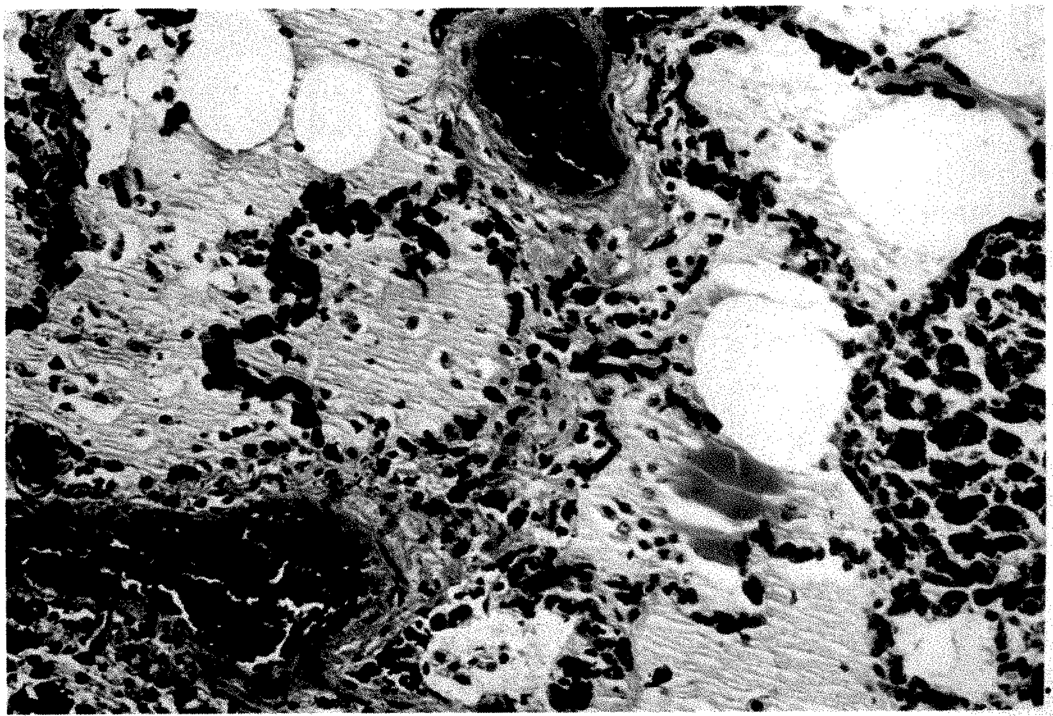

FIG. 3. Photomicrograph of lung from a 27-year-old, 472 lb patient with preoperative PaO_2 50 mmHg, $PaCO_2$ 48 mmHg, PAP 50 mmHg, PAOP 30 mmHg who died of presumed ventricular arrhythmia 5 weeks after gastric surgery. Note normal pulmonary arteries without medial muscular hypertrophy or intimal thickening (hematoxylin and eosin, original magnification ×150).

In these 18 patients, %IBW decreased from 224 ± 59 to 167 ± 57 ($p < 0.0001$), a 42 ± 19% loss of their excess weight. This weight loss was associated with significant ($p < 0.0001$) improvements in PaO_2 (from 50 ± 10 to 69 ± 14 mmHg) and $PaCO_2$ (from 52 ± 7 to 42 ± 4 mmHg) as shown in Figure 4. In this subset of the OHS group, pulmonary hypertension was present in 17 and was severe ($PAP \geq 40$ mmHg) in seven (Fig. 5). Seven of these patients had left ventricular dysfunction. The PAEDP exceeded PAOP by 5 mmHg in 13 patients. After weight loss and in association with improved arterial blood gases, PAP fell (Fig. 5) from 36 ± 14 mmHg to 23 ± 7 mmHg ($p < 0.0001$) and PAOP fell from 17 ± 7 mmHg to 12 ± 6 mmHg ($p < 0.01$). Pulmonary hypertension persisted in ten patients; however, none of them had a PAP >40 mmHg (Fig. 5). The PAOP was ≥18 mmHg in three of these patients with persistent pulmonary hypertension. There was no correlation between any measure of weight loss and postoperative PAP, PAOP, PaO_2, or $PaCO_2$. None of the 26 patients had clinical evidence of a pulmonary embolus and only the patient with the Miles® vena caval clip had lower extremity thrombophlebitis.

Of the 26 OHS patients, four with horizontal gastroplasty and three with vertical banded gastroplasty lost less than 40% of their excess weight and were subsequently converted to Roux-en-Y gastric bypass. One of these patients died on the sixth postoperative day from an occluded tracheostomy tube that had been reinserted because of recurrence of severe OHS and SAS. The remaining six patients, as well as the 19 others who underwent primary gastric bypass procedures, lost 67 ± 19% of their excess weight 1 year after gastric bypass and this weight loss has remained stable in all but two patients over a 3–6 year follow-up. The blood gas and pulmonary artery pressure data in this study were obtained after the first procedure. In three of these patients, blood gases deteriorated with weight regain and was associated with increased PAP and PAOP. These values improved again after renewed weight loss.

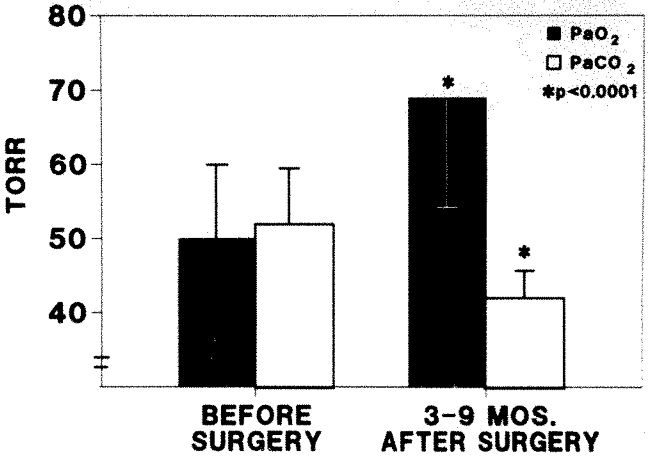

FIG. 4. Significantly improved PaO_2 and $PaCO_2$ in 18 patients 4–9 months after gastric surgery-induced loss of 42 ± 19% excess weight.

Case Reports

A 31-year-old white male taxi cab driver with a height of 74 inches weighed 590 lbs or 391 %IBW. He had been admitted on several previous occasions to the Medical Intensive Care Unit in heart failure necessitating urgent intubation and mechanical ventilation. He had severe SAS and had had several accidents as a result of falling asleep while driving his cab. Before surgery, his PaO_2 was 36 mmHg and $PaCO_2$ 57 mmHg. Following a 40-L diuresis, pulmonary artery catheterization revealed pressures of 75/34 mmHg with a PAOP of 12 mmHg. He underwent horizontal gastroplasty, tracheostomy, and insertion of a Miles® vena caval clip. He was able to be weaned from mechanical volume ventilation on the fifth postoperative day. Lower leg deep vein thrombophlebitis occurred after operation. Four months later, after losing 118 lbs, his PaO_2 had increased to 75 mmHg and $PaCO_2$ decreased to 43 mmHg. Repeat pulmonary artery catheterization revealed a pulmonary artery pressure of 40/20 mmHg with a PAOP of 10 mmHg. One year later he began to regain weight and was converted to a Roux-en-Y gastric bypass with further decrease in his weight to 240 lbs or 121 %IBW, which has been stable for 4 years. His sleep apnea is completely resolved, his PaO_2 is 85 mmHg and $PaCO_2$ is 39 mmHg. He now drives his cab without falling asleep at the wheel.

A 39-year-old black woman who is 62 inches tall and weighed 401 lbs (318 %IBW) had severe SAS with awake PaO_2 of 55 mmHg and $PaCO_2$ of 50 mmHg. Pulmonary artery catheterization revealed severe pulmonary hypertension (105/55 mmHg) and a sharply elevated PAOP (40 mmHg). Her cardiac output was 13 L/min/m^2. Before surgery an attempt was made to decrease her PAOP with furosemide; however, this was associated with a fall in cardiac output and systemic blood pressure necessitating volume restoration. She underwent tracheostomy, Roux-en-Y gastric bypass, and insertion of a Greenfield® vena caval filter. She was weaned off mechanical volume ventilation in 2 days and was discharged on the eighth postoperative day. Eight months after surgery, after losing 67 lbs (265 %IBW) her sleep apenea had completely resolved, her PaO_2 had risen to 83 mmHg; and her $PaCO_2$ had fallen to 44 mmHg. This was associated with declines in PAP to 35/29 mmHg, PAOP to 24 mmHg, and cardiac output to 8.6

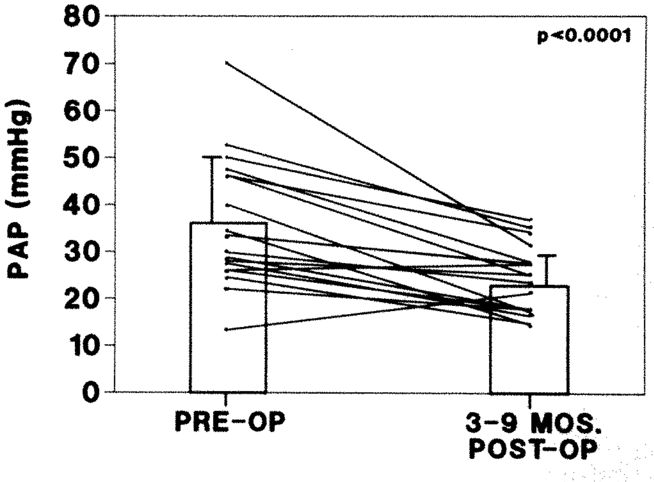

FIG. 5. Significantly improved mean pulmonary artery pressure (PAP) in 18 patients 4–9 months after gastric surgery-induced loss of 42 ± 19% excess weight.

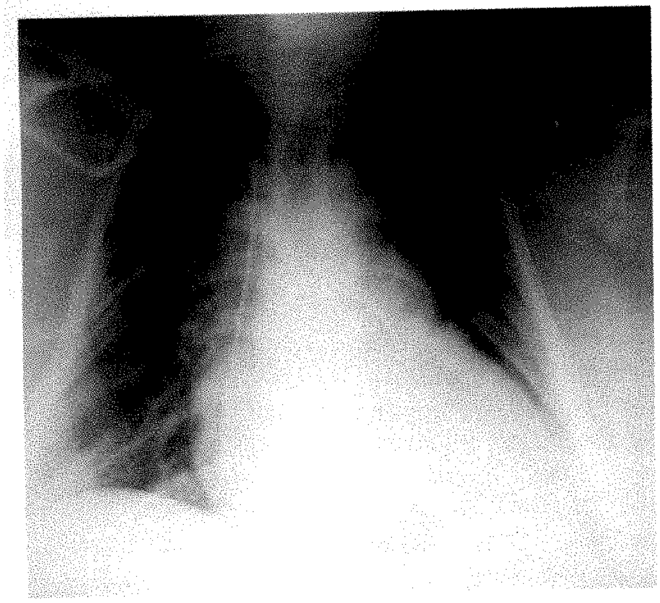

FIG. 6. Markedly enlarged cardiac silhouette on anterior-posterior portable chest roentgenogram before surgery in a 39-year-old, 62-inch tall, 401 lb black female with severe sleep apnea and awake PaO_2 55 mmHg, $PaCO_2$ 50 mmHg, PAP 105/55 mmHg, PAOP 40 mmHg, and cardiac output 13 L/min.

L/min. Her tracheostomy tube was removed and the stoma allowed to close. Three years after surgery she had lost 147 lbs (201 %IBW). At this time her PaO_2 was 95 mmHg and $PaCO_2$ was 39 mmHg. Repeat pulmonary artery catheterization revealed a PAP of 20/12 mmHg with a PAOP of 10 mmHg and 7 L/min cardiac output. A marked improvement in cardiac size can be seen by comparing her preoperative chest roentgenogram (Fig. 6) to one obtained 3 years later (Fig. 7).

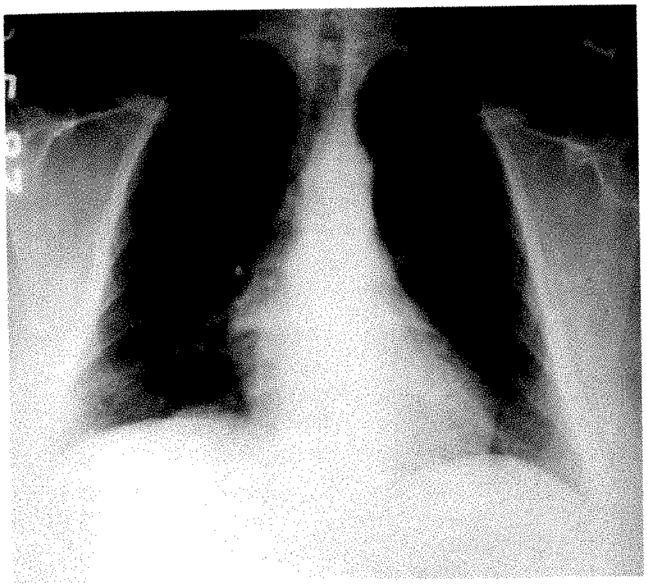

FIG. 7. Markedly improved cardiac silhouette on posterior-anterior chest roentgenogram 3 years after gastric surgery-induced 147 lb weight loss in patient from Figure 6 with correction of OHS: PaO_2 95 mmHg, $PaCO_2$ 39 mmHg, PAP 20/12 mmHg, PAOP 10 mmHg, and cardiac output 7 L/min.

Discussion

A recent consensus panel at the National Institutes of Health recognized morbid obesity as a serious medical problem in the United States,[25] affecting approximately 4.5 million persons.[26] Several studies have shown significantly increased mortality rates for the morbidly obese.[27-29] Cardiovascular disease accounts for most of this increase.[27] A subset of this population, comprising 12% of our patients who have undergone gastric surgery for morbid obesity, suffers from respiratory insufficiency of obesity, including the obstructive sleep apnea syndrome (SAS), the obesity hypoventilation syndrome (OHS), or a combination of the two.[1] Severe cardiac decompensation has been a prominent feature in many of these patients.[2-10]

This study found significant hemodynamic dysfunction in OHS patients compared with morbidly obese patients without respiratory insufficiency, including significantly higher pulmonary artery and pulmonary artery occlusion pressures. However, seven of the 20 control patients had mild pulmonary hypertension. Our initial intention was to determine the severity of presumed hypoxemic pulmonary artery vasoconstriction. Severe pulmonary hypertension was found in a large number of OHS patients; however, pulmonary hypertension appeared to be a result of both left ventricular dysfunction, as noted by an elevated PAOP, as well as pulmonary arterial vasoconstriction, where pulmonary artery end-diastolic pressures (PAEDP) were often more than 5 mmHg above the PAOP. Three patterns appeared to be present (Fig. 2): approximately one third had an elevated PAP entirely secondary to left ventricular dysfunction, since an increased PAEDP in these patients was within 5 mmHg of the PAOP; one third had pulmonary hypertension secondary to pulmonary vasoconstriction, since their PAOPs were normal; and one third had both left ventricular dysfunction (*i.e.*, PAOP $\geq$ 18 mmHg) and pulmonary vasoconstriction (*i.e.*, PAEDP > 5 mmHg above PAOP). Severe left ventricular dysfunction was seen in three patients with PAOP $\geq$ 30 mmHg in two and 40 mmHg in one. These values are consistent with a sharply decreased left ventricular compliance. Left ventricular dysfunction has been previously noted to be a significant component of heart failure in patients with OHS[5-10] and some have thought it highly unlikely that right ventricular failure could occur in these patients as an isolated event.[30]

The cause of left ventricular dysfunction in OHS could include a significant increase in central blood volume as a result of hypoxemic induced erythropoetin release. This would result in secondary polycythemia, leading to pulmonary venous and capillary congestion, and further hypoxemia. Increased central blood volumes have been found in morbidly obese patients with respiratory insufficiency[9,10] as well as in those with morbid obesity and systemic hypertension.[31] Patients with respiratory insufficiency of obesity were noted in our previous study to have a significant incidence of polycythemia that resolved with weight loss and correction of hypoxemia.[1] Although the mean hemoglobin level in the OHS patients in this study was normal, half of the patients were polycythemic, but there was no relationship between hemoglobin values and PAP or PAOP.

Other investigators have noted left ventricular dysfunction in morbidly obese patients without respiratory insufficiency.[32,33] Increased systemic arterial pressure could be responsible for left ventricular dysfunction. Marked increases in systemic arterial pressure have been noted during nocturnal hypoxemia associated with apneic episodes during sleep.[34] However, in this study, there were no significant differences in systemic arterial pressure or systemic vascular resistance index between the patients with OHS and the control group without respiratory insufficiency, suggesting that systemic hypertension was not responsible for the left ventricular dysfunction and that hypoxemia was not a significant determinant of systemic blood pressure in these patients.

Another possible mechanism for the severe left ventricular dysfunction noted in this study would be the hypoxemia itself. The heart extracts almost all of the oxygen presented to it during passage through the coronary circulation.[35] It is not surprising that these patients with extremely low PaO_2s (*i.e.,* high 30s or low 40s) might have left ventricular dysfunction. Myocardial oxygen delivery in these patients is probably made possible by increased levels of 2,3-diphosphoglycerate (2,3-DPG) with right-shifted oxygen hemoglobin equilibrium curves (increased P_{50}) and an increased ability to unload oxygen[36] as seen in high altitude[37] and patients with chronic hypoxemia.[38] We did not measure 2,3-DPG levels or P_{50} in these patients but often noted a much higher mixed venous oxygen saturation when measured with a co-oximeter than would be expected for the PvO_2 calculated from the Severinghaus nomogram.

In addition to left ventricular dysfunction, pulmonary arterial vasoconstriction contributed to pulmonary hypertension in approximately two-thirds of these patients. Hypoxemia is a known cause for pulmonary arterial vasoconstriction, which probably evolved from a need to shift pulmonary blood flow from diseased to healthy pulmonary segments. Hypoxemic vasoconstriction is an important feature of pulmonary hypertension associated with chronic obstructive pulmonary disease that can be relieved by oxygen supplementation.[39] Hypoxemic pulmonary artery vasoconstriction has also been shown to occur during nocturnal apneic episodes in patients with SAS.[34] Correction of sleep apnea in the 17 patients with both OHS and SAS in this series by weight reduction may have contributed to the improved pulmonary artery pressures as tracheostomy has been shown to improve nocturnal pulmonary hypertension by improving oxygen saturation.[34]

Our previous studies have documented a significant improvement in arterial blood gases, lung volumes, polycythemia, and sleep apnea after gastric surgery-induced weight loss.[1,12] Improvement in sleep apnea after surgically induced weight loss has also been documented by other studies.[40-42]. This study now documents an improvement in both pulmonary hypertension and left ventricular filling pressure associated with partial correction of abnormal arterial blood gases within 3–9 months after gastric surgery-induced weight loss. The absence of pulmonary arterial medial muscular hypertrophy or intimal thickening in the patient who died 5 weeks after surgery (Fig. 3) supports the reversibility of the pulmonary hypertension in these patients. In several patients who continued to lose weight, further hemodynamic improvement has been noted. Partial correction of the pulmonary hypertension and cardiac dysfunction in OHS also have been noted by others following medically induced weight loss.[43-45]

A number of patients in this study failed their gastric surgical procedure. These failures included both horizontal[15,16] and vertical banded gastroplasties.[17] Conversion to gastric bypass was associated with resumed weight loss. Gastric surgery for morbid obesity has been evolving rapidly over the past 20 years. Several procedures, especially horizontal gastroplasty[15,16] and gastric banding,[46] have been recommended in the literature but have subsequently been proven to be ineffective.[14,46] In a randomized prospective study, we found that Roux-en-Y gastric bypass was significantly more effective than the newer vertical banded gastroplasty, particularly for patients addicted to sweets.[20] In a more recent study, selective assignment of patients, *i.e.,* sweets eaters (80%) to gastric bypass and non–sweets eaters (20%) to vertical banded gastroplasty, we found that the gastric bypass patients lost, on the average, 67% of their excess weight and vertical banded gastroplasty patients lost 56% of their excess weight.[47]

Our experience confirms that surgery can be performed safely in critically ill morbidly obese patients if appropriate precautions are taken. These include preoperative pulmonary artery catheterization, careful anesthetic management, tracheostomy or nasal CPAP for patients with severe SAS, and postoperative mechanical volume ventilation with patients in a deep reverse Trendelenburg position until arterial blood gases on room air with a T-piece return to preoperative values and the patient can generate an adequate inspiratory effort and vital capacity. These patients are at great risk for fatal pulmonary embolism[11,24] and every effort must be made to minimize this risk with preoperative phlebotomy in polycythemic patients, use of intermittent venous compression boots, insertion of a Greenfield® vena caval filter in patients with severe pulmonary hypertension (PAP ≥ 40 mmHg), and early ambulation.

In conclusion, severe pulmonary hypertension is a frequent finding in morbidly obese patients with respiratory insufficiency and appears to be a result of both left ventricular dysfunction and pulmonary vasoconstriction. Gastric surgery for weight loss provides significant improvement in both the gas exchange and hemodynamic abnormalities associated with respiratory insufficiency of obesity.

Acknowledgments

The authors thank Gary Benton, M.D. for his assistance with data retrieval, Gordon E. Madge, M.D. for the pulmonary pathological evaluation and photomicrography, and the nurses, dieticians, and house staff of the Medical College of Virginia for their dedicated assistance in the management and postoperative evaluation of these challenging patients.

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DISCUSSION

DR. LAZAR J. GREENFIELD (Ann Arbor, Michigan): I would like to congratulate Dr. Sugerman and his associates on their results and thank him for an opportunity to review the manuscript.

The morbidly obese patient is a social outcast, and some of that stigma in the past was conferred on surgeons who tried to rearrange the GI tract in order to help these patients lose weight. The recent change in this attitude is a result of careful clinical studies as typified by today's presentation.

Dr. Sugerman has identified a subset of these morbidly obese patients with varying degrees of pulmonary hypertension, ventricular dysfunction and hypoventilation. These disturbances were reversed by partial weight loss that left them much less obese but not normal, and this raises several questions.

First, is there a threshold of weight gain which produces these changes incrementally? That is, does the left ventricular dysfunction precede the pulmonary hypertension or does hypoxemia initiate the changes with pulmonary hypertension?

Secondly, have you characterized the left ventricular dysfunction further? Is it a global or a regional wall motion abnormality, and is fatty change of the myocardium involved?

Third, are either of the hemodynamic abnormalities treatable preoperatively, such as with the use of additional oxygen to ameliorate the pulmonary hypertension, or the use of inotropic agents or vasodilators to improve left ventricular performance?

Also, is there a change in respiratory drive in patients with elevated $PACO_2$ that would make it dangerous to reverse their hypoxemia?

Surgeons have always realized that the obese patient represents a high risk for general anesthesia and a major operative procedure, but now there is physiological proof of serious hemodynamic changes in these patients, as well as improved techniques to promote weight loss and reversal of the changes.

DR. FRANK G. MOODY (Houston, Texas): This is a disease that likely has a very strong genetic component. The animal work, for example, with well defined obese species of rats and mice clearly shows a genetic background, and in the human, it appears to be reflected in some expression of lack of ability to handle excess calories with a meal. The phenotype is probably expressed through an inability to expand excess calories through thermogenesis.

People who weighed 200, 300, 400, or 500 pounds are *supposed* to weigh that. We are trying to develop strategies to bring them down to what would be more consistent with a perceived norm in order to ensure a long and healthy life, but we are not yet sure whether we prolong life in these patients by making them thinner.

This study clearly shows that the weight itself does not appear to be the only risk factor in most of these patients. It seems to be related to other factors that lead to pulmonary dysfunction, and the biggest culprit is the cigarette.

I have performed an obesity operation on 500 patients without a mortality, and I thought that was pretty good surgery. But on reflection, 400 of these patients were operated on in Salt Lake City, primarily nonsmoking Mormons. Now, 100 have been operated on in Houston where most people seem to smoke, but with comparable results. My own clinical experience does not provide a clear answer. There was no mortality in this group either.

Out of this experience, I have five patients that had this syndrome that, until I read Dr. Sugerman's paper a couple of nights ago, I didn't know really existed. Two of these patients had a rather difficult time in the intensive care unit during the post-operative period. The knowledge derived from this paper would have allowed us to identify those people preoperatively.

I would ask Dr. Sugerman for an algorithm. Which patients should have pulmonary function studies, and which should then have invasive monitoring for postoperative care? And, in addition, would he also be a little bit more specific in terms of the role of the cigarette in his own population?

DR. JAMES PAT O'LEARY (Dallas, Texas): Obesity is a disease. When I first presented a paper dealing with this topic, a gentleman approached the podium and said, "Do you really believe that obesity is a disease?" And when I said, "Yes," he sort of huffed and went back to his seat.

I think that in this particular study we have another physiologic study that demonstrates that obese people are different.

I have a couple of comments to make. The sudden death syndrome is real, and it occurs in obese people after cholecystectomy or after surgery for morbid obesity.

Left ventricular dysfunction was present in more than half of these patients. Harvey, was there dysfunction in your control group, also? And what about the right ventricle? Was it also abnormal?

The other and final comment is: People seem to get better when they lose weight, but your patient improved after getting down to 470 lbs, whereas other patients demonstrate the disease at 300 pounds. When they lose a small amount of weight, they seem to improve, and yet when they have lost a large amount of weight, they are better. They gain back an increment, and they get rose again. So I guess I am asking: Why do they get better? Is it simply a matter of mass, or is it something else that we don't understand?

DR. RICHARD J. FIELD, JR. (Centerville, Mississippi): I have had my life endangered many times by reckless taxicab drivers. I don't think I have had the experience of having one go to sleep on me as yours did.

We, too, have been interested in obesity surgery for many years, and I think, Dr. Sugerman, this is a classic paper. I am sure that part of my opinion is a bit colored by my having had some of my training at the Medical College of Virginia, but this documentation of a fact that we already knew will be very helpful to us in obesity surgery. I haven't seen these figures before.

The Pickwickian Syndrome is something we are all familiar with, and we, too, noticed that in our series of 578, 28% of these people exhibited this strange phenomenon. It has been very gratifying to find that, as he mentioned, even where there was a small amount of weight loss, rather marked improvement was shown.

It has been our opinion that these symptoms seem to be on the basis of mass, but some other factors have come out of your study that make it interesting for us to look to the future.

The other classic part of this paper is that, for the first time, I sense a truly serious approach to the surgery of the obese has been taken.

As Dr. Greenfield mentioned, these people suffer greatly, much more, I think, than the general public and the surgical profession has understood. They truly are a diseased group, and we are now looking at them and taking obesity surgery seriously, rather than through the tongue-in-cheek approach we had taken originally.

We had a very graphic case of Pickwickian Syndrome several years ago. A man in his fifties weighed 478 pounds. He exhibited the symptoms that you discussed in your paper. Arrangements were made for his surgery. The surgery was scheduled. The week before he was to come in for his surgery, this man was found at the base of a deep crevice; he had been driving alone, and there was no other vehicle. Obviously, he had gone to sleep at the wheel.

We were too late, but thank you very much for a great bellwether for obesity surgery.

DR. HERSCHEL A. GRAVES (Nashville, Tennessee): I rise primarily to congratulate Harvey Sugerman on an excellent presentation of a good piece of work, and then to say that Frank Moody took my questions.

Harvey's work supplies data that explain the mechanics of the obesity hypoventilation syndrome. I remember that when Lynwood Herrington first began his jejunoileal bypass series 20 years ago, he performed tracheostomies on all patients. Everyone anticipated postoperative respiratory difficulties in the extreme form. It very soon became obvious that energetic routine pulmonary toilet care was sufficient and the tracheostomies weren't necessary. However, all surgeons, anesthesiologists, and their hospital staffs involved in obesity surgery still "run a bit scared" and work hard at postoperative lung care.

I have performed about 300 gastric stapling procedures and we have had no deaths and no serious pulmonary problems.

I have had only one true Pickwickian patient, and he weighed 489 pounds preoperatively. On the third postoperative day in the intensive care unit, after motioning to me for 48 hours to pull his endotracheal tube, he pulled it himself and said, "Doc, I have got to get up and walk around." So he did, and proved to us that his very poor blood gases were tolerated quite well by someone who was so accustomed to the abnormal oxygenation.

I also wonder about the tobacco. In my experience, without having a count, very few morbidly obese patients smoke. I wonder if one of your statisticians could go back and determine if the patients with poor arterial gases are smokers. I think that might be an interesting added factor in this analysis.

This is an excellent piece of work, Harvey.

DR. HARVEY SUGERMAN (Closing discussion): I would like to thank all the discussants, but I would particularly like to thank Dr. Greenfield for his support. When he was at the Medical College of Virginia, I proposed to him my interest in pursuing surgery on these patients. He said, "By all means, go ahead, but make sure you study what you are doing." This was excellent advice for a new faculty member and was very helpful to me.

There were several questions with regards to the threshold weight. Certainly a number of these patients will improve markedly with a very small amount of weight loss. However, without performing heart catheterization monthly, it was not possible in this study to determine the threshold weight. A few patients improved significantly but did not return to normal by the time of restudy, although they corrected the abnormal pulmonary gas exchange and hemodynamic dysfunction completely over several years. Pulmonary hypertension did not correct in the early postoperative period with mechanical ventilation and correction of the hypoxemia, so there is more than just pulmonary hypoxemic vasoconstruction going on. One patient died suddenly five weeks after surgery. This lady had had multifocal PVC's prior to surgery and was on quinidine. Surprisingly, her pulmonary arterioles were normal at autopsy, since I had predicted pulmonary arterial intimal hyperplasia.

It is very difficult to determine if the cause of cardiac dysfunction is secondary to problems with the left ventricle, the right ventricle, or both. Increased systemic afterload is one possibility. Patients with obstructive sleep apnea will have systemic hypertension during their obstructive episodes and hypoxemia. The PA and wedge pressures have also been found to go up as their systemic pressure rises. However, our patients had no difference in systemic pressure compared to the morbidly obese controls, so increased afterload was not the cause of left ventricular dysfunction in our patients.

Polycythemia and increased central blood volumes have also been incriminated, but there was no correlation in this study between hemoglobin and pulmonary artery pressure. Perhaps it is a problem with an increased pulmonary afterload, dilatation of the right ventricle, and shift of the interventricular septum to the left, with a decreased left ventricular end diastolic volume. Some of these patients had PaO_2's in the high 30's and low 40's. Since the heart extracts all the oxygen that it gets, the heart may not be getting enough oxygen and develops a stiff, poorly compliant myocardium that takes weeks or months to repair. We have no data regarding whether hypoxemia precedes or is subsequent to left ventricular dysfunction, but I presume it is the former. In the future, we plan to obtain MUGA scans of both the right and left ventricles pre- and postweight reduction surgery.

In response to Dr. O'Leary's questions, mild left ventricular dysfunction was also noted in our morbidly obese control group without respiratory insufficiency. We have also found that ventricular function improved in this group following surgically induced weight loss. Sudden death syndrome has been seen in four of our more than 700 morbidly obese patients following obesity surgery: one at 3 days without known pre-existing heart disease; one at 5 weeks in the patient described in our report who had pre-existing arrhythmias and respiratory insufficiency; one at 5 months in a patient with idiopathic hypertrophic subaortic stenosis, and one at 1 year in a patient with muscular dystrophy who required a pacemaker for complete heart block prior to obesity surgery. Postmortem examinations were performed in three of these patients and did not reveal a cause of death. A prolonged QT interval seen in morbidly obese patients and associated with sudden death was not noted in any of these patients.

We have not studied the use of inotropic or vasodilator agents in these patients. We have tried to diurese them and remove presumed excess intravascular volume. This was tried in the patient with the wedge pressure of 40. However, diuresis was associated with a decreased cardiac output and required volume re-expansion. This patient probably had a stiff, poorly compliant ventricle and needed a high wedge pressure to maintain adequate left ventricular end diastolic volume and cardiac output.

Giving supplemental oxygen did not diminish respiratory drive, and several were treated with nocturnal oxygen.

I certainly agree with both Dr. Moody and Dr. Graves that most of these patients had an additional pulmonary problem. 80% of these patients were smokers, in contrast to 10% of the morbidly obese control group. So, as far as the lungs are concerned, it may be all right to be morbidly obese, and it is certainly not all right to smoke, but when one does both, then there is a real problem. A second pulmonary problem on the top of obesity tips the scale.

With regard to management algorithms, pulmonary function tests have been interesting, but have not been very helpful as a routine preoperative evaluation. I think all morbidly obese patients should have a preoperative arterial blood gas determination. A history of having fallen asleep at the wheel, heavy snoring, waking up with headaches, very restless sleep, or multiple awakenings strongly suggest obstructive sleep apnea syndrome. These patients should undergo preoperative sleep polysomnography. Trauma surgeons must be alert to the patient who is injured in an automobile accident and is suspected of having fallen asleep at the wheel. We used to perform a tracheostomy on all patients with severe obstructive sleep apnea. But we treat them now with nocturnal nasal CPAP, which is a mask that fits over the nose and corrects the obstructive episodes. If they won't tolerate nasal CPAP and they have severe sleep apnea with cardiac arrhythmias, they need a tracheostomy. If the patient has hypoxemia and/or hypercarbia when awake, the patient should undergo right heart catheterization. If their mean pulmonary artery pressure is very high, that is, >40 mmHg, a Greenfield filter should probably be inserted.

Anesthesia in these patients is potentially very dangerous. However, we have not had a life-threatening anesthetic event in any of our morbidly obese patients, including those with respiratory insufficiency. We usually have three anesthetic personnel available: one to hold the mask, one to squeeze the bag, and one to help administer medications. Awake intubation is usually very traumatic and, in our experience, unnecessary.

Postoperatively, these patients should be kept in the reverse Trendelenburg position to maximize diaphragmatic excursion. Venous compression boots are used to counteract the increased venous pressure and reduce the risk of thromboembolism. A volume ventilator is used until the patient's blood gases return to their preoperative hypoxic, hypercarbic state. If you wait until they completely correct their hypoxia, you will have a long wait. But eventually these problems will be resolved, with the weight loss making the surgery truly lifesaving in this high risk group of patients.

Resection of Hepatic Duct Bifurcation and Transhepatic Stenting for Sclerosing Cholangitis

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Thirty-one patients with sclerosing cholangitis underwent reconstruction of their hepatic duct bifurcation and long-term stenting between 1980 and 1987. Indications for surgery were persistent jaundice in 29 and recurrent cholangitis in two. The mean serum bilirubin level before surgery was 10.4 mg/dl. Liver biopsy revealed that 26 patients had varying degrees of hepatic fibrosis, and five patients had progressed to secondary biliary cirrhosis. In 29 patients the major obstructive duct disease was at or near the hepatic duct bifurcation, and in two patients it was in the distal common duct. The operative procedure consisted of: (1) excision of the hepatic duct bifurcation and extrahepatic biliary tree, (2) dilatation of the intrahepatic ducts, (3) insertion of Silastic transhepatic biliary stents, and (4) bilateral hepaticojejunostomies. Two of the five patients (40%) with cirrhosis died after surgery. In contrast, only one of 26 patients (3.9%) with hepatic fibrosis died after operation. The 1-, 3-, and 5-year actuarial survival rates for patients with cirrhosis were 20%, 20%, and 20%, respectively. The only long-term survivor underwent a liver transplant. The 1-, 3-, and 5-year actuarial survival rates for patients with hepatic fibrosis were 92%, 87%, and 71%, respectively. In addition, the mean serum bilirubin levels of patients with hepatic fibrosis at 1, 2, 3, 4, and 5 years were 3.4 mg/dl, 2.9 mg/dl, 4.0 mg/dl, 5.4 mg/dl, and 4.3 mg/dl, respectively. Two of the long-term survivors subsequently underwent a liver transplant. Patients with sclerosing cholangitis, persistent jaundice, and biliary cirrhosis should be referred for consideration of liver transplantation. However, in the absence of biliary cirrhosis, if the major obstructive disease is at the hepatic duct bifurcation, primary biliary reconstruction and long-term stenting should be considered.

SCLEROSING CHOLANGITIS is an idiopathic disease presenting with multiple inflammatory strictures of the biliary tree, usually involving both the intra- and extrahepatic bile ducts, and often most severe at the hepatic duct bifurcation.[1] The disease generally presents with jaundice and pruritis. Despite its name, episodes of fever usually occur only after operation or nonoperative biliary intervention. The disease is seen most commonly in middle-aged males, often with associated inflammatory bowel disease.[2-4] The clinical course of sclerosing cholangitis is usually episodic, and quite variable. However, in most series the disease has generally been progressive, eventually leading to secondary biliary cirrhosis and hepatic failure. A variety of treatment regimens ranging from anti-inflammatory and immunosuppressive drugs to liver transplantation have been tried. In 1983, in a small series of patients, we reported a surgical approach consisting of excision of the hepatic duct bifurcation and extrahepatic biliary tree, dilatation of the intrahepatic ducts, and long-term stenting with Silastic transhepatic stents.[5] We have continued to treat patients with sclerosing cholangitis with this same regimen, and herein report our experience with a total of 31 patients.

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Clinical Material

Between 1980 and 1987, 31 patients with sclerosing cholangitis underwent primary biliary reconstruction. These 31 patients were selected from a group of approximately 100 patients with sclerosing cholangitis seen at Johns Hopkins during this interval. Ninteen patients were men, 12 were women, and the mean age was 44.7 years (range: 21–71 years). Twenty-seven of the patients were white and four were black. The diagnosis of sclerosing cholangitis was made in all patients on the basis of multiple preoperative precutaneous and endoscopic ret-

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TABLE 1. *Sclerosing Cholangitis (N = 32)*

Admission Laboratory Data	
Bilirubin (NL 0.3–1.2 mg/dl)	10.4 mg/dl (1.0–50.0 mg/dl)
Alkaline phosphatase (NL 30–120 IU/L)	528 IU/L (144–1860 IU/L)
SGOT (NL 0–35 IU/L)	146 IU/L (35–413 IU/L)
SGPT (NL 0–30 IU/L)	171 IU/L (39–696 IU/L)

rograde cholangiograms. In addition, numerous cholangiograms obtained at prior surgical procedures were reviewed. In all instances, multiple biliary strictures were present, involving both the intra- and extrahepatic biliary tree. In no patient could operative injury or biliary calculus disease be considered a major factor in the genesis of the inflammatory strictures. In addition, cholangiocarcinoma was subsequently ruled out in all patients because the entire extrahepatic biliary tree was excised and examined histologically in each instance. Two patients with sclerosing cholangitis who underwent biliary reconstruction were excluded from this series, when at the time of surgery they were found to have an associated proximal biliary tumor.

Disease duration was often difficult to determine. However, it was estimated to have ranged between 1 month and 13 years, with a mean duration of 3 years. Fourteen of the 31 patients had biopsy-proven inflammatory bowel disease, and eight of these patients had undergone bowel resection. Ten of the 14 patients with inflammatory bowel disease had ulcerative colitis, and four had Crohn's disease. Four of the patients (one with Crohn's disease, three with ulcerative colitis) had ileostomies at the time of biliary reconstruction for their sclerosing cholangitis. One patient with ulcerative colitis had had a colectomy for carcinoma. Four patients with sclerosing cholangitis had chronic pancreatitis, as evidenced by a clinical history of multiple episodes of abdominal pain and hyperamylasemia, and confirmed by gross findings at the time of surgery for sclerosing cholangitis.

TABLE 2. *Sclerosing Cholangitis (N = 31)*

	No. of Patients
Indications for surgery	
Persistent jaundice	29
With cholangitis	11
Recurrent cholangitis	2
Area of major duct involvement	
Bifurcation	29
Distal common duct	2

Nineteen of the 31 patients had undergone prior biliary tract surgery at other institutions. These procedures included cholecystectomy, insertion of a T tube, choledochoduodenostomy, and choledochojejunostomy. Nine of the 31 patients had undergone intra-abdominal procedures for other than biliary tract disease, in most instances bowel resections for inflammatory bowel disease. Many patients had been treated medically for sclerosing cholangitis before referral to The Johns Hopkins Hospital. In most instances the drug was a steroid (12 patients), or azathioprine (6 patients), but a variety of other medications including cholestyramine and D-penicillamine had been used.

At the time of admission for biliary reconstruction, the serum bilirubin level among these 31 patients ranged from a low of 1.0 mg/dl to a high of 50 mg/dl. The mean bilirubin level at the time of admission was 10.4 mg/dl. Alkaline phosphatase level ranged from a low of 144 IU/L to a high of 1860 IU/L, and averaged 528 IU/L. The SGOT ranged from a low of 35 IU/L to a high of 413 IU/L and averaged 146 IU/L. The SGPT ranged from a low of 39 IU/L to a high of 696 and averaged 171 IU/L (Table 1). Liver biopsies were obtained from all patients either before operation or at the time of surgery. Twenty-six patients had varying degrees of fibrosis, but five patients had clearly progressed to secondary biliary cirrhosis.

The indication for surgical intervention in 29 patients was persistent jaundice (Table 2). This was defined as a bilirubin level of 5 mg/dl or greater persisting for at least a 3-month period. Eleven of these 29 patients, all of whom had had prior biliary tract surgery, also had recurrent bouts of cholangitis. Two patients, in the absence of persistent jaundice, had recurrent bouts of cholangitis as their indication for surgical intervention. All patients had intra- and extrahepatic biliary duct involvement, and in 29 patients the bifurcation was severely involved (Fig. 1). In the remaining two patients the area of most severe involvement was the distal common duct.

Before surgery, 19 of the 31 patients at the time of percutaneous transhepatic cholangiography had Ring catheters inserted into the intrahepatic biliary tree, and passed down through the areas of stricturing into the duodenum (Fig. 2). In eight of the 19 patients only one Ring catheter was inserted, generally into the right hepatic duct, but in 11 patients both the right and left intrahepatic ducts were cannulated percutaneously. Ring catheters were inserted before operation in only five of the first 15 patients operated on before 1983 for sclerosing cholangitis. However, 14 of the last 16 patients, operated on since 1983, have had catheters inserted, and in nine of the 14 patients the catheters were placed bilaterally. These catheters were placed before operation not to decompress the obstructed biliary tree, but to (1) aid in the dissection of the hepatic duct bifurcation at the time of surgery; (2) to assist in dilating the intrahepatic ducts at the time of surgery; and (3) to aid in the placement of the Silastic transhepatic biliary stents.

Operative Procedure

Patients were explored through a right subcostal incision. The extrahepatic biliary tree was identified, and if the gallbladder had not previously been removed, a cholecystectomy was performed. The common duct was dissected free and encircled with a vessel loop. Often because of prior surgery as well as inflammatory changes in the duct, identification of the extrahepatic biliary tree would have been difficult if a Ring catheter had not been placed before operation. As soon as the common duct was encircled, it was dissected distally to where it passed posterior to the duodenum. At this point the distal common duct was divided, the Ring catheters extracted from the duodenum, and the distal common duct oversewn. The proximal biliary segment, with the Ring catheters acting as a guide, was then carefully dissected up to the hepatic duct bifurcation. The hepatic duct bifurcation was easily identified by palpatating the divergence of the two Ring catheters. The bifurcation was dissected both anteriorly and posteriorly by reflecting the proximal biliary segment in a cephalad direction. The Ring catheters aid greatly in retracting the proximal biliary segment, as well as in identifying and dissecting out the right and left hepatic ducts. When the bifurcation has been dissected, the right and left hepatic ducts are divided and the extrahepatic biliary tree removed from the operative field.

As described in our last communication, if Ring catheters are not present, the right and left hepatic ducts are carefully and tediously dilated with the use of Bake's dilators.[5] This maneuver has to be performed carefully because if a false passage is made, and the Bake's dilator passes through the wall of the intrahepatic ductal system, further dilatation up into the intrahepatic biliary tree is impossible. With Ring catheters in place, this dilatation can be performed rapidly, safely, and without the risk of a false passage. Dilatation is performed by suturing progressively larger Coude catheters to the Ring catheter, and withdrawing the Ring catheter out the top of the liver, thereby progressively drawing larger catheters up through the intrahepatic biliary tree, and thus dilating it. Generally a #12 F Coude catheter is sutured to the Ring catheter and pulled up into the intrahepatic biliary tree first. A #14 F Coude catheter is then sutured to the #12 F catheter and used to further dilate the biliary tree. This is followed by pulling up a #16 F Coude catheter, and then finally the #18 F Silastic transhepatic biliary stent. These maneuvers are performed over a guidewire, so that if a catheter breaks or becomes unsutured, the tract is not lost. This progressive catheter dilatation has made what in the past has been a relatively

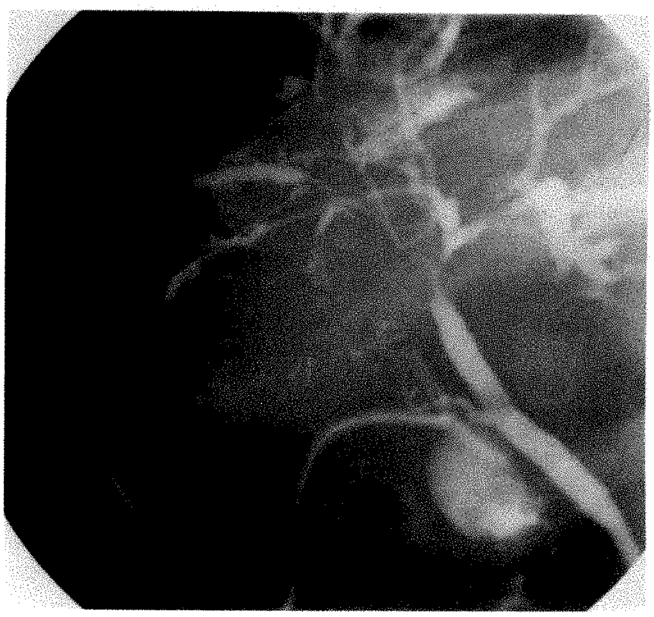

FIG. 1. Percutaneous transhepatic cholangiogram of a patient with sclerosing cholangitis and with persistent jaundice, with the most severe disease being at the hepatic duct bifurcation. Note that the T tube, inserted at another institution, has been displaced.

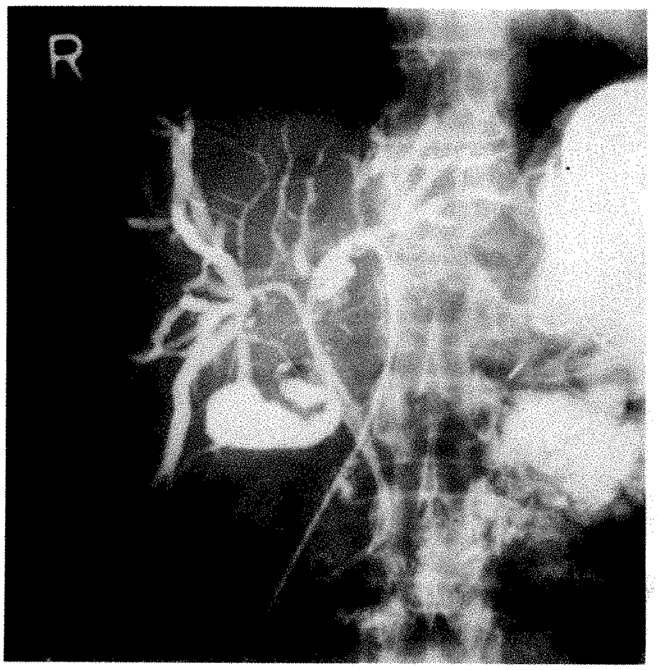

FIG. 2. A patient with sclerosing cholangitis, persistent jaundice, and severe bifurcation involvement. Ring catheters have been inserted percutaneously before operation, to serve as technical aids at the time of surgery.

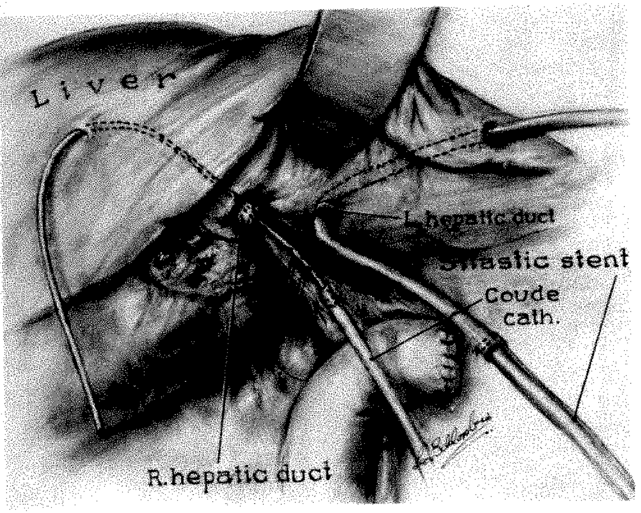

FIG. 3. Progressively larger Coude catheters are sutured, first to the Ring catheter, and then to each other,, and are drawn up through the biliary tree, thereby dilating it. Finally, a Silastic transhepatic biliary stent is sutured to the last Coude catheter, and is drawn into place.

unsafe and uncertain dilatation, into a safe and certain way to ensure dilatation of the intrahepatic ducts (Fig. 3).

Silastic transhepatic biliary stents were placed in 30 of the 31 patients. In one of the two patients with only a distal biliary stricture, a T-tube was used. In six patients only one stent was inserted, generally because one lobe was atrophic and not believed to be worth decompressing or because the biliary tree was so strictured in one lobe that it could not be intubated. In 19 patients, bilateral transhepatic biliary stents were inserted, and in five patients three stents were used. In the five patients in whom three stents were inserted, two stents were placed on the right side, one in each major segment. A Roux-en-Y jejunal loop 60 cm in length was then constructed. The Roux-en-Y loop was brought up into the right upper quadrant in a retrocolic position. One, two, or three hepaticojejunostomies were then performed, depending on how many major lobar or segmental hepatic ducts had been intubated with Silastic transhepatic biliary stents. The Silastic stents extended into the Roux-en-Y loop for approximately 10–15 cm. That portion of the Silastic stent that resided in the Roux-en-Y loop and in the intrahepatic ductal system, contained multiple side holes. That portion of the Silastic stent that exited through the diaphragmatic surface of the liver was brought out through a stab would either in the right or left upper quadrant. The stents were sutured securely to the skin with two stainless steel wires. The hepaticojejunostomies and stent exit sites were drained with drains brought out through stab wounds in the upper abdomen.

Clinical Course

In all 31 instances the resected specimens revealed benign inflammatory disease. Three patients died after operation, for a hospital mortality rate of 9.7%. Two of these three patients were among the five patients who had established biliary cirrhosis (hospital mortality rate of 40%). Among the remaining 26 patients with varying degrees of hepatic fibrosis, there was only one death for a hospital mortality rate of 3.9%. The three patients died 31, 37, and 60 days after surgery of liver failure and sepsis. Two of the patients who died developed hematobilia after operation, secondary to an hepatic artery portal venous fistula that required control *via* percutaneous embolization. This occlusion of hepatic arterial inflow to the liver may have further hastened their development of liver failure.

The convalescences of the 28 patients who were discharged from the hospital were prolonged but relatively uneventful. Three of the patients had continued episodes of cholangitis that required prolonged antibiotic administration to control. One patient developed a subhepatic collection after surgery that was drained percutaneously. A final patient with an unrecognized cardiomyopathy required treatment for pulmonary edema after operation. The average hospital stay of the 28 patients who were discharged from the hospital was 28 days. However, over the past 3 years during which an effort has been made to shorten the hospitalization of all surgical patients, the last seven patients have been operated on and discharged with an average length of stay of 15 days.

Among the three patients with biliary cirrhosis who were discharged from the hospital, two died of liver failure, 6 and 8 months after discharge. The only patient among the five patients with biliary cirrhosis who survived long term underwent liver transplantation 2.5 years after his reconstructive biliary surgery. He continues to lead an active life after liver transplantation 80 months after his initial biliary tract reconstruction.

The 25 patients without biliary cirrhosis who were discharged from the hospital have fared much better. The mean serum bilirubin level of this group of patients before surgery was 9.9 mg/dl. At 12 months after surgery the mean serum bilirubin level was 3.4 mg/dl, at 24 months 2.9 mg/dl, at 36 months 4.0 mg/dl, at 48 months 5.4 mg/dl, and at 60 months 4.3 mg/dl (Fig. 4). The changes in alkaline phosphatase and serum transaminase levels were less impressive (Fig. 5). Two of these 25 patients subsequently underwent successful liver transplantation, 48 and 80 months after biliary reconstruction, because of progressive liver disease. One patient is alive and well 93 months after her initial reconstruction. The second patient died of chronic rejection 1.5 years after her transplant. There have been six additional deaths among these 26 noncirrhotic patients. Five of the deaths have been from chronic liver failure, and the sixth was from metastatic lung cancer.

The Silastic biliary stents have been left in permanently to prevent restricturing within the major intrahepatic ducts (Fig. 6). The stents are changed over guidewires as an outpatient procedure every 3 months. An occasional patient because of excessive sludge formation will require stent changes as often as every 6 to 8 weeks. Episodes of fever have been unusual, and generally signify that a stent change is needed.

Mean follow-up for the entire group is 3.5 years. The mean survival for all 31 patients is 42 months, with a median survival of 44 months. Actuarial survival rates at 1, 3, and 5 years are 80%, 76%, and 63%, respectively. Among the five cirrhotic patients, mean survival is 19 months with median survival of 6 months. Actuarial 1-, 3-, and 5-year survival rates are all 20%. Among the 26 patients without cirrhosis, mean survival was 46 months, with median survival being 48 months. Actuarial 1-, 3-, and 5-year survival rates are 92%, 87%, and 71%, respectively (Fig. 7).

Discussion

Because sclerosing cholangitis is episodic in nature, has an extremely variable course, and is an uncommon disease, natural history data are difficult to obtain. The best data suggest that the disease proceeds slowly and inevitably to the point where in many patients biliary cirrhosis will develop and hepatic failure ensue.[2,3] One recent study, however, suggests that this scenario may not be as inevitable as previously believed.[6] All of these uncertainties make therapeutic interventions particularly difficult to evaluate. Steroids have been the mainstay of treatment for this disease almost from the time it was described. However, no data from any institution have established their efficacy in a broad group of patients. Other drugs such as azathioprine, D-penicillamine, and colchicine have been used, but again no convincing data support their benefit.

In several institutions, including our own, percutaneous intubation of the biliary tree and balloon dilatation

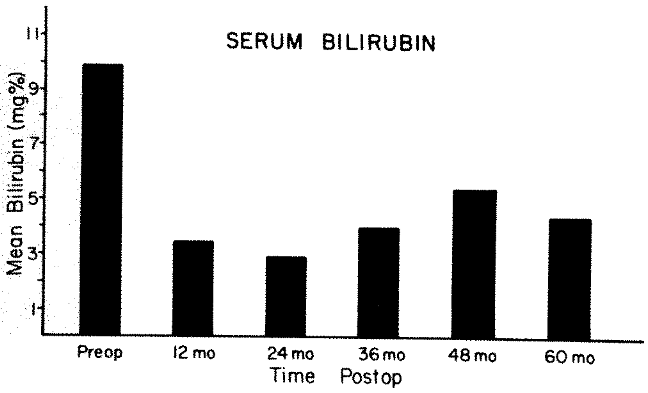

FIG. 4. Serum bilirubin levels before and after surgery for the 26 patients with hepatic fibrosis (before operation N = 26, 12 months N = 21, 24 months N = 20, 36 months N = 18, 48 months N = 13, 60 months N = 12).

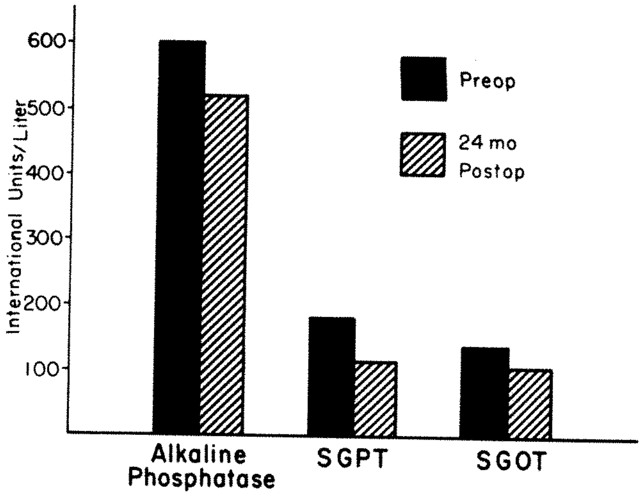

FIG. 5. Serum alkaline phosphatase, SGPT, and SGOT levels before and after surgery for the 26 patients with hepatic fibrosis (before operation N = 26, 24 months N = 20).

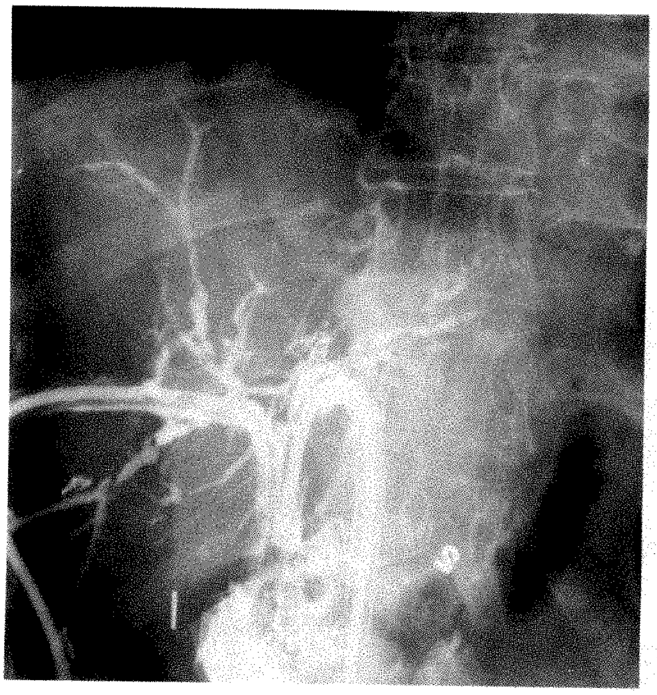

FIG. 6. Postoperative cholangiogram after bifurcation reconstruction demonstrating the biliary drainage achieveable with this procedure.

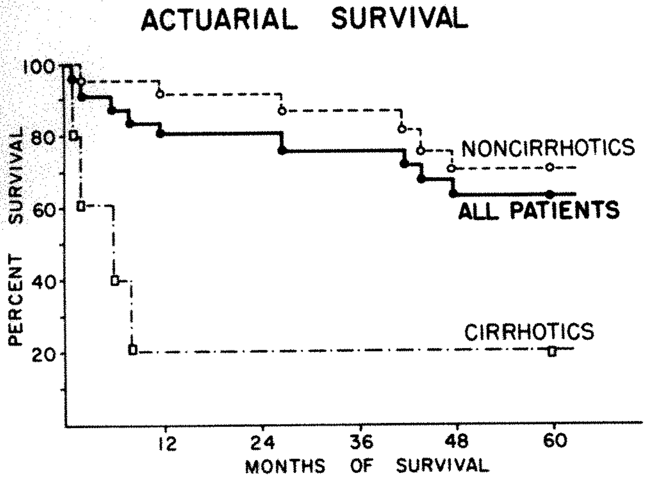

FIG. 7. Actuarial 5-year survival curves for the 31 patients with sclerosing cholangitis undergoing reconstruction of the hepatic duct bifurcations (all patients N = 31, noncirrhotics N = 26, cirrhotics N = 5).

have been used for iatrogenic strictures.[7] This technique has recently been extended to patients with sclerosing cholangitis. However, the strictures in sclerosing cholangitis often do not lend themselves to this approach. The biliary tree with its multiple fibrotic branches can be difficult to intubate either percutaneously or endoscopically. Moreover, multiple procedures and, sometimes, general anesthesia are required with balloon dilatation. Thus, in our experience, this course of therapy has frequently been unsuccessful and/or not well tolerated. Others have suggested operatively resecting the distal biliary tree and performing a hepatico- or choledochojejunostomy to a Roux-en-Y loop. The end of the Roux-en-Y loop is then brought out as a cutaneous or subcutaneous stoma to provide access for postoperative catheter balloon dilatation of intrahepatic strictures. In one report of 16 patients managed with this approach, results have been moderately encouraging in noncirrhotic patients.[8]

The recognition and documentation that the strictures in sclerosing cholangitis are often most severe in the area of the bifurcation, as reported from this institution,[1] has led to a new surgical approach reported first in 11 patients in 1983.[5] Although others had recognized in the past that severe stricturing often occurred at or near the hepatic duct bifurcation, its functional significance had not been recognized because of the failure of the fibrotic intrahepatic biliary tree to dilate. In 1983, we suggested that these bifurcation strictures were functionally significant, and that the disease might be treated effectively by resecting the hepatic duct bifurcation, dilating the intrahepatic biliary tree, and permanently stenting the ductal system with Silastic transhepatic biliary stents. Because it was believed that the stricturing would recur if the Silastic stents were removed, our approach was to leave them in permanently. Among the 11 patients initially reported, one patient died after operation without leaving the hospital. Among the remaining 10, seven are still alive. Three patients eventually required hepatic transplantation because of progressive liver disease, and two of these three remain among the seven still surviving. Mean follow-up of this group of 11 patients now extends to 64 months.

Hepatic transplantation remains another option for the management of patients with sclerosing cholangitis. A large experience has been obtained in Pittsburgh, and sclerosing cholangitis is now the third most common indication for liver transplantation in adults at that institution.[9] Transplantation is a big operative procedure that requires chronic immunosuppression. However, at a certain stage of the disease it remains the only and an excellent option. Nevertheless, the risks of hepatic transplantation are still such that if it can be avoided, or put off, and other alternatives made available, many believe that would be a preferable option.

A recent report from the University of Pittsburgh documents that 1- and 3-year survival rates are 71% and 57%, respectively, among 55 patients undergoing liver transplantation for sclerosing cholangitis.[9] In the current series of 31 patients undergoing resection of the hepatic duct bifurcation and transhepatic stenting, 1- and 3-year survival rates are 80% and 76%, respectively. However, in the 26 noncirrhotic patients, survival rates are 92% and 87% at 1 and 3 years, respectively. This group of noncirrhotic patients may not be directly comparable to patients with established cirrhosis who undergo liver transplantation. However, the results obtained in these noncirrhotic patients may suggest that our surgical approach is warranted in this subset of patients.

Our operation is only palliative and will be of benefit only if large duct obstruction plays a significant role in the progressive liver disease that patients with sclerosing cholangitis experience. In our series three patients required liver transplantation because of progressive liver failure. The transplants were successful in all three patients. Moreover, in the University of Pittsburgh series prior biliary tract surgery did not adversely influence long-term survival.[10] Thus, if our approach is not successful, hepatic transplantation remains a viable option.

The current series of patients suggests that the option of excising the hepatic duct bifurcation in the face of persistent hyperbilirubinemia and major stricturing in this area, along with dilatation of the intrahepatic biliary tree and permanent stenting, is an alternative that has a great deal of appeal. If one excludes patients who before operation are demonstrated by needle biopsy to have cirrhosis, the operative procedure can be done with a very low hospital mortality. Furthermore, with the use of Ring catheters placed percutaneously before operation, the hepatic duct bifurcation can be identified, dissected, and readily excised. In addition, with the Ring catheters in place, the operative dilatation of the intrahepatic biliary tree can be quickly and safely accomplished. Finally, by the long-term use of operatively placed Silastic transhepatic biliary stents, restricturing can be avoided. The demonstration that this operative procedure can result in a marked and persistent lowering in serum bilirubin, and an excellent 5-year actuarial survival, speaks in favor of this approach.

Our current approach is to follow patients with sclerosing cholangitis without specific therapy as long as persistent hyperbilirubinemia does not develop. When persistent hyperbilirubinemia develops, as defined by a serum bilirubin level of 5 mg/dl or greater for at least 3-months, percutaneous liver biopsy should be performed. If there is any question about the right lobe being atrophic, then the left, or perhaps both lobes, should be biopsied. If biliary cirrhosis is present, the patient should be referred for consideration of hepatic transplantation. If biliary cirrhosis is not present, and cholangiography demonstrates severe stricturing at or near the hepatic bifurcation, or in the distal biliary tree, we believe that primary biliary reconstruction should be considered. The approach of excising the hepatic duct bifurcation and the extrahepatic biliary tree, dilatation of the intrahepatic biliary tree, and long-term stenting can provide such a patient with good quality long-term survival. If the patient does not respond to this primary procedure, or subsequently the liver disease progresses and jaundice recurs and/or biliary cirrhosis develops, liver transplantation can still be performed. We believe such an approach does not preclude, but may well postpone, or even avoid in some instances, the need for liver transplantation.

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DISCUSSION

DR. RONALD K. TOMPKINS (Los Angeles, California): Dr. Cameron and his group have done their usual fine job in presenting the results of a successful treatment of a very difficult disease.

We at UCLA have had similar experiences with this disease in the past, and we agree with their thesis that operative therapy in the proper patient is far superior to medical therapy for sclerosing cholangitis.

I do have some questions that I hope that the group will address in their closing remarks.

First, in reviewing the manuscript last evening, I noticed that there were 100 patients at Hopkins during this period of time with the diagnosing of sclerosing cholangitis. Of these, only 31 were selected for operation, and I wonder if the authors would tell us what their specific selection criteria are. I think that would be very helpful to us.

Secondly, it has been difficult for us to determine at what time after the onset of obstruction of the biliary tract that secondary biliary cirrhosis develops. I wonder if the authors could give us some clues as to the time frame for the development of biliary cirrhosis.

Thirdly, amongst radiologists, there is an interest now for percutaneous dilatation of these strictures and for nonoperative treatment of this disease, and I wonder what the experience has been at Hopkins with this method and whether they are considering this as an alternative in the management of these patients.

I think Dr. Cameron mentioned that these transhepatic stents stay in permanently, and I wonder if he could tell us what the incidence of cholangitis and septic complications is with those permanent in-dwelling tubes.

Finally, I would agree with the authors that the patient who is clearly defined as cirrhotic at the outset of the evaluation should be referred directly for a liver transplantation.

Liver transplantation is often a difficult operation in itself, and when there has been previous biliary tract surgery done, it makes the transplant much more difficult and increases the operative morbidity and mortality risk.

I enjoyed the presentation of this very nice paper, and I appreciate the authors' giving me the opportunity to review the manuscript.

DR. KENNETH W. WARREN (Boston, Massachusetts): About two years ago I promised myself that I would never discuss another paper on this subject.

Having recently written another chapter, and standing here today to discuss this paper, just shows that my word is not reliable, especially when I make a vow to myself.

Over the years, I have had a considerable experience with this disease. It is a disease of unknown etiology, despite its frequent association with inflammatory bowel disease.

It has no distinctive pathologic features. There is no satisfactory medical treatment. Initially, we who had been treating this disease for 30 or 40 years were rather tentative in our surgical approach. I think what Dr. Cameron and his group have shown here today indicates that an aggressive approach to a special type of sclerosing cholangitis, where the major lesion is at the bifurcation, will be a definite advance. Furthermore, long-term stenting is going to become increasingly popular. With the interventional radiologist doing such resourceful work in some of these patients, as Dr. Tompkins said, any operation on sclerosing cholangitis should assure a premanent approach to these ducts so that the radiologist can manipulate them more frequently.

Someone has already mentioned Ernie Ring. He takes care of one of my patients who has had multiple operations. Since he has been taking care of him—dilating ducts and replacing tubes—the patient's jaundice has disappeared.

One of the difficulties, of course, as we talk about liver transplants, is when to make the decision to perform the transplant. Dr. Cameron pointed out that if the patient is developing progressive cirrhosis, that probably is the time. I think it is very difficult to say this is correct, because the interval that a patient may undergo with no symptoms, or relatively minor symptoms, may be long. I have had one patient go 19 years without symptoms, but when he returned he had such progressive cirrhosis and portal hypertension that he was not a candidate for liver transplantation.

Having started this discussion by saying that I promised myself never to talk or write about sclerosing cholangitis again, I hope that Dr. Cameron and his group, as well as others, will continue to study this problem.

DR. JOHN W. BRAASCH (Boston, Massachusetts): I appreciate this opportunity to discuss this paper.

When Dr. Cameron speaks about intubation of bile ducts with Silastic tubes with or without operation, I listen, because he has had perhaps the largest experience—in this country and outside this country—with this particular technique in managing strictures.

Sclerosing cholangitis, as has already been pointed out several times this morning, is a kind of mystery disease. The preoperative diagnosis is strictly radiologic. We don't know the cause; and then the condition shades off into carcinoma of the duct, primary biliary cirrhosis, traumatic strictures, and chronic stone cholangitis. In fact, recently it has been pointed out that patients with AIDS may show this very peculiar type of bile duct reaction.

Our experience parallels Dr. Cameron's except that we have perhaps paid more attention to the presence of a major stricture than to the presence of cirrhosis. We try to save as much of bifurcation as one can, and it is possible in some of these patients not to remove the whole extrahepatic biliary system there, and thus get away with a lesser resection.

We do use the anastomosis, and we do stent, but perhaps for not as long as Dr. Cameron does, because we are a little afraid of the complications of chronic stenting.

In concluding, I would like to ask one question, and that is: How do you recognize the cirrhosis that would point you more towards a liver transplant than a reparative operation? We have had problems with biopsy material in estimating the degree of cirrhosis. In our experience, a small piece of tissue frequently does not give you the whole picture of the liver.

I have enjoyed this paper very much.

DR. C. RANDLE VOYLES (Jackson, Mississippi): I, too, have watched the work of Dr. John Cameron since the early 1980's and I applaud him for his update today.

He has been a pioneer in the work of the surgical approach to sclerosing cholangitis, and I have applied some of the concepts that he has utilized in Jackson, Mississippi, my first exposure being with Les Blumgart in London.

The basic concept is to transplant when the liver damage is irreversible; if you have hepatic reserve with a bad extrahepatic duct, then replace the extrahepatic duct.

I have two questions based on my experience with these patients. Number one, we know cirrhotics don't do well with any operation, much less extrahepatic duct replacement. Of your noncirrhotic patients, can you look at the cholangiograms and predict which patients are going to do well? I suspect those with dilated intrahepatic ducts are a significantly different group from the patients that have diffuse intrahepatic disease.

Secondly, what is the natural history of your noncirrhotics that have the operation? You have presented data regarding bilirubin out to five years. How quickly do these patients develop frank cirrhosis, impaired liver function, and portal hypertension? I suspect on the basis of your preoperative cholangiograms that you may be able to identify some long-term winners; how many of your patients are well at five years?

DR. HARVEY J. SUGERMAN (Richmond, Virginia): Two years ago before the society, we presented data on extrahepatic biliary obstruction secondary to chronic pancreatitis, and I notice from this presentation that four of the 31 patients had biliary obstruction secondary to chronic pancreatitis, and I would like to have just a little better feel for what evidence of sclerosing cholangitis was present in that group of patients, since extrahepatic biliary obstruction secondary to chronic pancreatitis is a very common event.

I presume that this was a totally separate subgroup of that group of patients; and secondly, it has been my impression from our liver transplanters that certainly the greatest difficulty (the greatest blood loss) has been in those patients who have had to have their liver transplants after one or more previous operative procedures. I just wonder about the difficulties in patients who have undergone their transplantation and have previously undergone this operative procedure in terms of the technical difficulties and blood loss in that group of patients, and wonder if it wouldn't have been better to use percutaneous biliary dilatation with Ring catheters.

DR. JOAQUIN S. ALDRETE (Birmingham, Alabama): I think Dr. Cameron's paper is not only very important, but also timely because, at the present time, one of the greatest decisions concerning patients with sclerosing cholangitis is whether to send them directly to liver transplantation or treat them by some other operative method.

Having the advantage, or perhaps the misfortune, of being involved in our institution in both of these methods of treatment with such patients, I would like to offer some comments and ask a question of Dr. Cameron. I totally agree with his criterion for selection of patients to be treated without transplantation. It seems to me that there are two types of patients with sclerosing cholangitis. First, there are those that have a rather rapid progression into the terminal states of the disease. They promptly develop biliary cirrhosis, and there is no question that such patients should directly go the route of hepatic replacement.

Other patients, however, have a slower course in the deterioration of their hepatic function, and, particularly if they have segments of dilated bile ducts, our experience, (although with a smaller number of cases), has been similar to that reported by Dr. Cameron. These patients with sclerosing cholangitis that have localized segments of stenosis, usually located near the area of the bifurcation, are the ones that can be treated by intubation.

We have seen four such patients that we have followed from one to six years after doing a similar intubation procedure, with the only difference being that the stents we used were completely internal and permanently implanted. I have been very satisfied with the results obtained with these patients.

In these days, the identification of this small but existent population of patients is important because there is a tendency to send all patients with sclerosing cholangitis directly to the transplant team. Although the results are spectacular when the transplant works, one must remember that there is still 20–30% mortality, and the survivors require per life immunosuppression that is sometimes expensive and cumbersome. Although I am one of the greatest enthusiasts of liver transplantation, I think the possibility of safely postponing or avoiding it, with the patient alive and functioning, should be pursued.

The careful and precise operative technique described by Dr. Cameron can help prevent some of the technical problems if subsequent transplantation was required. I noticed that he percutaneously places a catheter in the bile duct so that it can be readily identified. He cuts the bile duct very early and does all the dissection very close to the hilum of the liver, leaving the portal vein and the hepatic artery relatively undisturbed to facilitate their discussion when subsequent transplantation of the liver is required.

The problem is in selecting the patients for the intubation method, but Dr. Cameron has been very specific in his criterion.

Another problem is that some of these patients develop or have carcinomas of the bile ducts concomitant with the primary sclerosing cholangitis. In fact, the last patient in whom we performed a transplantation for this disease had a carcinoma of the bile ducts that we could not detect before operation. So, my question to Dr. Cameron is:

How often have you seen carcinomas in these patients? Again, I congratulate you on a superb piece of work and for pointing out that there are checks and balances, and that not everything is clear-cut in the operative treatment of sclerosing cholangitis.

DR. HENRY A. PITT (Closing discussion): Dr. Tompkins asked about the selection criteria. Patients were selected for this operation if they had persistent jaundice or recurrent cholangitis and the major point of obstruction was near the hilum or more distally. In general, we have reserved this operation for patients with a total bilirubin of more than 5 mg/dL that persists for at least 3 months. In only two of our patients was the indication for surgery recurrent cholangitis without persistent jaundice.

Dr. Tompkins also asked about balloon dilatations as a treatment for patients with sclerosing cholangitis. Over the past 8 years, we have managed approximately 20 patients at Johns Hopkins with percutaneous transhepatic balloon dilatation of biliary strictures. Most of these strictures have been postoperative, whereas only two patients with sclerosing cholangitis have been initially managed with this technique. Both of these patients had persistent symptoms and eventually came to surgery. Moreover, we have been impressed that balloon dilatation can be quite painful. As a result, several patients have requested general anesthesia when repeat dilatations were recommended. Thus, if a nonoperative technique requires multiple procedures and anesthetics, we wonder whether one operation isn't better.

Three of the 31 patients had problems with cholangitis after surgery. These episodes usually result from tube occlusion and can be managed with tube change and a short course of systemic antibiotics. Most of the patients have their tubes changed electively every 3 or 4 months and do not take oral antibiotics in the interim. However, three of our patients have required more frequent tube changes and chronic oral antibiotics to prevent recurrent cholangitis.

Several discussants asked about hepatic transplantation, and their questions implied that morbidity and mortality of liver transplantation might be increased if the patient has had prior biliary surgery. In discussions with Dr. Starzl, he states that the operation is technically more difficult if the patient has had prior biliary tract surgery. However, in terms of 3- and 5-year survival, the bottom line seems to be unaffected by prior biliary surgery in adults with sclerosing cholangitis. Yet at the University of Pittsburgh, prior surgery for biliary atresia does adversely affect the long-term outcome of liver transplantation in children with this problem.

Dr. Warren and others asked about the etiology of sclerosing cholangitis. A growing body of data now suggest that the etiology of sclerosing cholangitis is multifactional and that sclerosis of the bile ducts may represent the end-stage of many diseases. In some patients, including those with inflammatory bowel disease, the etiology may be an autoimmune phenomenon. In a small percentage of patients, bacterial infections or congenital anomalies may result in sclerosing cholangitis. We have also described patients with both histiocytosis X and sclerosing cholangitis. Recent data, including some from AIDS patients, also suggest that viral infections can result in sclerosing cholangitis. Presently, we are treating the end-stage of this disease. We need to learn more, however, about the etiology so that we can eventually develop specific therapies to prevent the problem.

Dr. Warren and others asked about the use of long-term stents and the timing of liver transplantation. We have left the stents in our patients indefinitely to provide access for removal of biliary sludge or stones. Postoperative balloon dilatation of intrahepatic strictures can also be accomplished via these access ports. With respect to subsequent liver transplantation, the indications for these patients are the same as for those without prior surgery. In general, these patients become candidates for transplantation when they have established cirrhosis and progressive liver failure. One pitfall to be aware of, however, in diagnosing secondary biliary cirrhosis is the atrophy/hypertrophy complex. Some of these patients with long-standing obstruction of only one side of the liver will develop cirrhosis in one lobe and hypertrophy in the other. Thus, if the right lobe is atrophied and biopsy from that lobe demonstrates cirrhosis, an additional biopsy from the left lobe may be necessary to provide the entire picture.

Dr. Braasch suggested that his approach is very similar to ours. I believe I have already answered his question about cirrhosis. Obviously, we rely upon the expertise of our hepatic pathologists, who review these biopsies very carefully and help us to make clinical decisions.

Dr. Voyles asked whether we can predict outcome from the patient's cholangiographic pattern. The one group that has done well uniformly is the small subset of patients in whom the disease involves primarily the common bile duct. Some, but not all, patients with diffuse intrahepatic involvement have had a poor outcome. Thus, despite moderate intrahepatic disease, if the patient has a major point of hilar or extrahepatic obstruction but no evidence of cirrhosis on liver biopsy, we would recommend our biliary reconstructive approach. In some patients, we have even observed improvement of the intrahepatic cholangiogram after surgery.

Dr. Voyles also asked about the quality of life of the long-term survivors. The majority of these patients are really quite well. They have their tubes changed three or four times a year, but this procedure is frequently done on an outpatient basis.

Dr. Sugerman asked about the four patients with associated chronic pancreatitis. These patients had typical sclerosing cholangitis with strictures above the intrapancreatic portion of the bile duct. Many patients with sclerosing cholangitis have sludge in their bile ducts as a result of the strictures and stasis. We believe that passage of this debris may cause a "gallstone" type of pancreatitis. In addition, the biliary strictures associated with this disease may also involve the sphincter mechanism. One or both of these factors may cause pancreatitis in patients with sclerosing pancreatitis. Moreover, by dividing the bile duct and diverting the flow of bile, our operation may actually prevent ongoing "gallstone" pancreatitis.

We would agree with Dr. Aldrete that both biliary tract surgery and hepatic transplantation should be available for patients with sclerosing cholangitis. We are performing both procedures at Johns Hopkins. We recommend transplantation for patients with established cirrhosis. However, this procedure and the associated immunosupression have real morbidity and mortality. Therefore, we feel that biliary reconstruction is preferred for patients who have not yet progressed to cirrhosis.

Dr. Aldrete also commented on concomitant cholangiocarcinomas. We have presented 31 patients. However, two additional patients not included in this series were initially thought, on the basis of their cholangiograms and other clinical data, to have sclerosing cholangitis. At surgery they had cholangiocarcinomas at the hilum, in addition to sclerosing cholangitis. We believe that this association is another reason why patients should be managed initially with resection of the hepatic duct bifurcation and biliary reconstruction, rather than with either balloon dilatation or hepatic transplantation.

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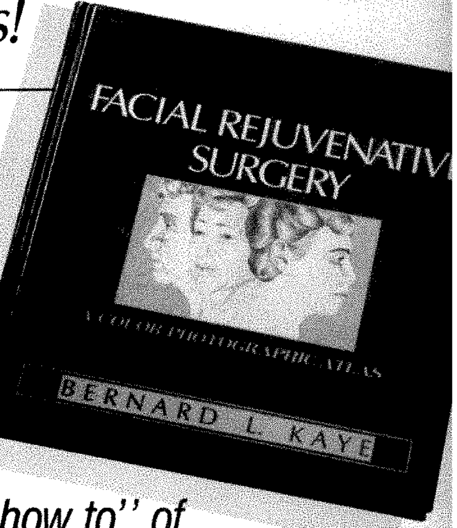

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About the author

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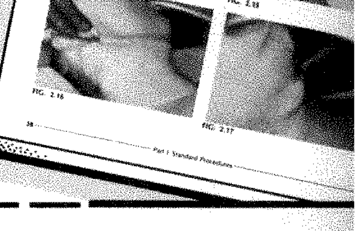

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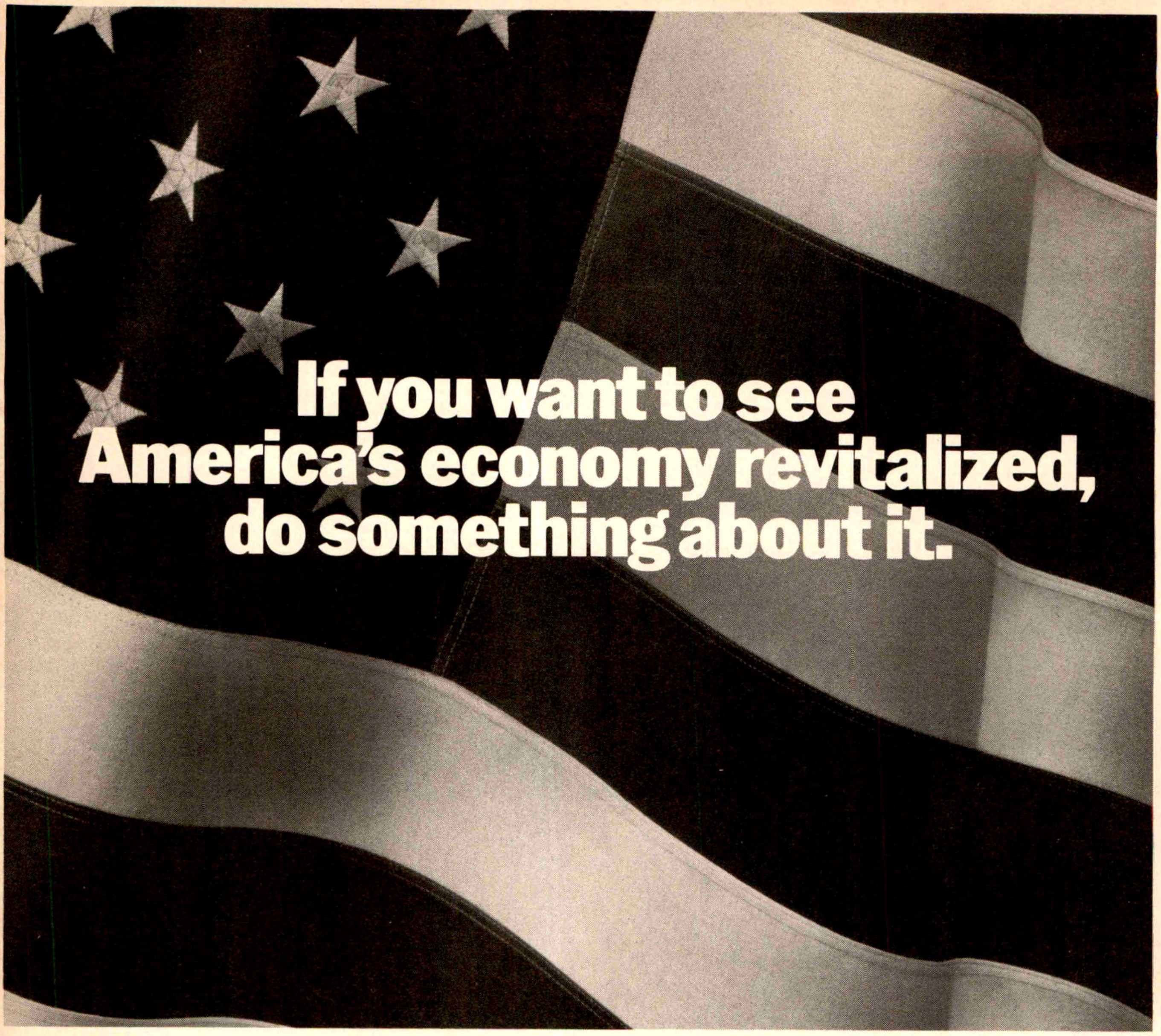

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Management of Variceal Bleeding in Patients with Noncirrhotic Portal Vein Thrombosis

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Since 1971, 70 patients have been seen at Emory University Hospital with gastroesophageal varices secondary to extrahepatic portal vein thrombosis (PVT). Thirty-seven of these patients had had prior major operative therapy. In only three patients (8%) was shunt surgery successful, and there was a high incidence of rebleeding, other morbidity, and mortality. Of especial note are the serious consequences of simple splenectomy; splenomegaly and thrombycytopenia should rarely, if ever, be used as indication for splenectomy in portal hypertension. In 1977, the use of selective distal splenorenal shunt (DSRS) was begun at Emory in this population and a selective shunt has been possible in 24 of 29 patients (83%) who had had no prior operative therapy. Results have been excellent with a greater than 90% patency rate, long-term portal perfusion in all, no encephalopathy, and late rebleeding in one patient. Quantitative studies at 3–6 years show stability of liver function, significant decrease in spleen size, and rise in platelet count. However, long-term follow-up (>15 years) is required in PVT patients before definitive assessment can be obtained. A specific problem of the PVT patient is late shunt stenosis which requires close observation; dilatation of the shunt was performed in six of the 24 patients with a patent shunt. Poor results with non-shunt operative procedures in PVT were again documented. The proper role of endoscopic variceal sclerotherapy is not yet clear, but appears to be an excellent addition to the therapeutic options. In conclusion, for patients with a patent splenic vein, initial therapy should be a selective shunt; for patients without a patent splenic venous system, endoscopic sclerotherapy is the procedure of choice.

EXTRAHEPATIC PORTAL VEIN THROMBOSIS (PVT) in the noncirrhotic is a relatively uncommon cause of portal hypertension in this country. Effective management of bleeding varices in PVT patients is especially important as progressive liver deterioration with death from hepatic failure is not the limiting factor in survival, as in patients with cirrhosis, chronic active hepatitis, or other severe hepatic disease. When first seen, PVT patients are usually young, in good general health, and capable of normal educational and work achievements if variceal hemorrhage is controlled and therapeutic endeavors do not induce other serious problems.

In earlier papers we and others have emphasized the unique physiology of PVT patients as related to liver blood flow.[1-3] To most surgeons a diagnosis of portal vein thrombosis signifies an absence of portal perfusion of the liver and there is no concern about shunting all portal flow into the systemic venous circulation.[4-11] The portacaval, mesocaval, and central splenorenal shunts are examples of this type of operation, which we refer to as total shunts. In 1893, Pavlov and his associates published a paper in which they studied the Eck fistula (portacaval shunt) in dogs.[12] In this paper they defined clearly the syndrome of portal-systemic encephalopathy and this aspect of the work is often cited in the literature. They also studied carefully an interesting subset of animals, those which survived and prospered, regaining their normal health; autopsy studies revealed occluded or markedly stenosed shunts in all. Also noted was the development of large *hepatopetal* collateral veins (the portal vein was ligated as part of the Eck operation) which restored some portal perfusion of the liver. They concluded that a modicum of portal venous blood perfusing the liver was necessary to ensure health and long-term survival of these experimental animals.

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The human with extrahepatic portal vein thrombosis fits this model, with high pressure in the general portal venous system (including the spleen), a normal hepatic sinusoidal pressure and *hepatopetal* collateral flow. The pattern in cirrhosis is markedly different with a high hepatic sinusoidal pressure and *hepatofugal* collaterals. When the hepatic sinusoidal pressure is essentially the same as splenic pulp pressure, there is no hemodynamic predisposition for collateralization to the liver *versus* the spleen. This latter hemodynamic pattern is seen after a selective distal splenorenal shunt (DSRS) in patients with PVT. In patients with PVT, hepatopetal collaterals are easily demonstrated by angiography and are usually designated "cavernous transformation of the portal vein." One aim of this study is to determine if long-term hepatic portal perfusion is sustained after DSRS in patients with PVT and if such flow is clinically relevant.

It is well known that splenectomy will alleviate the pancytopenia of portal hypertension.[5,7,8] However, splenectomy is rarely indicated because the risk of the splenomegaly and pancytopenia is low, and the risk (acute and chronic) of the operation is high. In addition, in some patients, the splenic vein is the only portal tributary suitable for shunting and splenectomy leads to loss of this option for control of variceal bleeding. As emphasized in many papers,[5,10,13] the most ill-advised of all interventions in portal hypertension is splenectomy for a low platelet count in a child with a patent splenic vein. A second question then arises: is splenectomy ever indicated in extrahepatic PVT?

There have been a number of groups advocating nonoperative therapy in patients with PVT,[14–17] because the tolerance for bleeding is great, and shunt failure has occurred historically in a high percentage of surgical patients. This position has been greatly strengthened by the reintroduction and marked improvement in endoscopic variceal sclerotherapy. The success at Emory of sclerotherapy for bleeding varices in other conditions has also stimulated our interest in the role of sclerotherapy in the management of patients with PVT.

Materials and Methods

This is a prospective but nonrandomized study of patients with portal hypertension and variceal bleeding secondary to extrahepatic PVT in the absence of cirrhosis, cancer, or other liver pathology, such as polycystic disease. We have also excluded two important related conditions, isolated splenic vein thrombosis and idiopathic portal hypertension (portal sclerosis). The purpose of this work is to reassess our previous concepts regarding pathophysiology, diagnosis, and management of PVT and extend the duration of our follow-up.

All patients were seen and studied at Emory University Hospital in Atlanta, a tertiary care referral center for adults. The first distal splenorenal shunt for PVT in Atlanta was performed in 1977, but we have elected to include all patients seen at this hospital since 1971, the year a general study of portal hypertension was begun.

Evaluation of patients included liver biopsy and angiography in addition to conventional clinical and laboratory procedures. Angiographic evaluation consisted of splenic and superior mesenteric artery injection with both arterial and venous phase filming. This was accompanied by hepatic and renal vein angiography and manometry; in some patients direct splenoportography was necessary for more accurate delineation of the venous anatomy. Endoscopic procedures were used frequently, both for diagnostic and therapeutic purposes. Quantitative tests followed a protocol previously published by us.[18] Liver function was assessed by galactose elimination capacity (GEC) and liver blood flow was measured by low-dose galactose clearance. The estimation of portal perfusion of the liver was limited to angiography following the departure to another University of the Faculty member responsible for our radionuclide technique. Cardiac output was measured by both echocardiography and radionuclide angiocardiography. Calculation of liver and spleen volumes by computerized tomography were also studied by techniques previously reported.[18] Assessment of encephalopathy included clinical evaluation, EEG, blood ammonia, and trail testing.[19]

A subset of six patients having DSRS have had preoperative and serial postoperative quantitative evaluation for up to 6 years. The purpose of this "in depth" study has been to document the hepatic function and hemodynamic effects of DSRS. These patients are believed to be representative of the overall DSRS group, and have been emphasized in this analysis because they have been available for repeated study of several years' duration.

Patient Population

Seventy consecutive patients with PVT admitted to Emory University Hospital since 1971 form the patient base for this investigation. Some general characteristics of these patients are presented in Table 1. One feature of crucial importance in management is the presence of a major tributary of the portal system that remains patent and functional. The two most important vessels in this regard are the splenic and superior mesenteric veins; also of value are gastroepiploic, left gastric, and inferior mesenteric veins. The analysis of our data may be somewhat anomalous in that 37 patients (53%) had undergone major operative therapy before being seen at Emory. In only three (8%) of these patients was there a normal tributary found, facilitating a DSRS in one patient and a mesocaval shunt in the two others.

Another important determinant in this group was absence of the spleen that was confirmed in 29 patients at the time of referral (Tables 1 and 2). In 24 patients, simple splenectomy had been performed (frequently as treatment for hypersplenism) and in five patients, a central splenorenal shunt had been attempted. Unfortunately in none of the patients having splenectomy in other hospitals do we have unequivocal data as to the state of the portal circulation before the splenectomy. Table 2 outlines the nature of the previous operations in this group.

In 33 patients there had been no prior major operative therapy and 29 of these were seen after the decision to use DSRS in PVT patient therapy. Selective shunts are the procedure of choice for our group as we attempt to achieve both decompression of gastroesophageal varices and maintainance of portal flow to the liver. In these 29 patients, some type of selective shunt was achieved in 25.

There was equal distribution between males (36) and females (34) and the mean age at the time of first admission to Emory was 35 years (Table 1). This in all probability reflects the adult nature of the patient population at Emory University Hospital since we do not have a pediatric service at this Institution. Patients who had had prior operative therapy at other institutions were about 10 years older than those first treated at Emory.

Results

The excellent long-term outlook of patients with PVT has been emphasized by some authors and questioned by others. Our population of older patients showed some hazards of the disease not often seen in children. These included venous infarction of the small bowel, death from pulmonary emboli, massive hemobilia, and late, severe encephalopathy requiring closure of a central splenorenal shunt. Nevertheless, the outlook for our PVT patients is certainly better than that of the patients with chronic liver disease, as more than 90% survive for 5 or more years after initial therapy.

Patients with PVT often appear to be in excellent health if seen before a complication arises. Careful study, however, reveals the liver to be smaller than normal, as is total hepatic blood flow. The liver biopsy results are essentially normal as are the ordinary liver test results. True liver function test results are on the lower side of normal.

TABLE 1. *General Characteristics of Total Patient Population*

Total population	70 patients
Males	36
Females	34
Mean (±SD) age (range)	34.9 ± 17.2 years (11–75)
Spleen in	41
Spleen out	29
Prior major therapy	37
No prior major therapy	33

TABLE 2. *Principle Procedures Performed in Patients Referred who had Received Prior Major Therapy*

Splenectomy	24
Splenectomy plus central splenorenal shunt	5
Splenopneumopexy	2
DSRS (thrombosed)	2
Mesocaval shunt (thrombosed)	1
Mesenteric thrombosis (resection)	1
Gastric devascularization	1
Exploration for shunt	1
Total	37

Mortality

Six of the 70 patients have died (Table 3). Two of the deaths were due to unrelated problems, cancer of the brain and pancreas. One was due to rebleeding, in a complex patient described below. There was a single operative mortality (1.8%) in a 62-year-old patient who had bled through sclerotherapy with a recent failed attempt at a portacaval shunt at another hospital. An urgent attempt to create a makeshift shunt was unsuccessful, and splenectomy (the splenic vein was thrombosed) and gastric devascularization were performed. He died in the hospital of bilateral pneumonia and general sepsis.

Therapies

The selection of type of intervention (if any) was determined by our assessment plan as shown in Figure 1. The results achieved with the patients in different ana-

TABLE 3. *Causes of Death and Duration from Main Management Method for Total Population*

1	44/F	Bleeding. Prior central SRS. Ligated. Awaiting sclerosis.
2	45/F	Pulmonary embolus. Devascularization 2 years prior.
3	62/M	Sepsis, post OP. Attempted shunt elsewhere. Splenectomy devasc.
4	63/M	Trauma/multiorgan failure. DSRS 6 months prior.
5	64/M	Carcinoma pancreas. Devascularization 4 years prior.
6	69/F	Brain tumor. Splenectomy/devascularization 3 years prior.

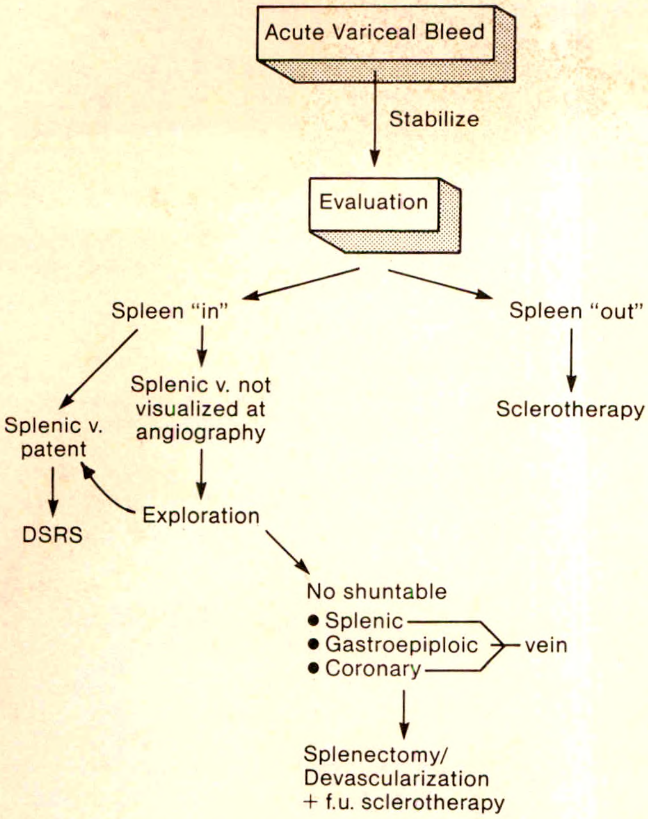

FIG. 1. A flow diagram showing our recommended management. Management options are dictated by prior surgical therapy and patency of portal venous tributaries.

tomical categories and prior therapies are as follows (Table 4).

Shunts

Selective shunts. Twenty-nine patients had exploratory surgery with intent to create a selective shunt, and in 25 this was successful. In the shunt group there were 19 DSRS, three distal splenocaval shunts, two gastroepiploic-renal, and one left gastric to renal shunt. One of the 19 DSRS was performed in a 20-year-old woman in whom a splenic transposition procedure (splenopneumopexy)[20] had been performed 20 years previously.

Patency of shunt. There was only one early thrombosis in the shunt group, a splenocaval anastomosis, for an overall patency rate of 96%. One DSRS had a successful early revision for a patent but kinked splenic vein, which had resulted in outflow obstruction and early postoperative bleeding. A rather specific problem in the PVT patients is the need for re-evaluation of the shunt at 3–6 months for possible stenosis. Patients whose splenic vein shows evidence of prior phlebitis are particularly at risk, and if stenosis is documented at shunt catheterization, dilatation of the anastomosis is indicated (Figs. 2 and 3). This was necessary in six of the 25 patients, a much higher incidence than seen following shunts for cirrhosis or other hepatic problems. Dilatation failed in one of the gastroepiploic shunts and revision of the anastomosis was required at 1 year. This increased tendency to stenosis is believed to be related to the thrombophlebitic process within the portal venous system. Our practice of interrupting the anterior row of sutures in the anastomosis probably facilitates the use of postoperative dilatation.

TABLE 4. *Definitive Bleeding Control, Deaths and Follow-up Status by Main Therapy Groups*

Management	No. of Patients	Rebleeding	Deaths	Loss to F/U
DSRS	25	1	1	1
Splenectomy	10	6	2	2
Devasc/sclerosis	10	5	3	2
Sclerosis	12	4	0	1
Makeshift shunt	4	3	0	0
Mesocaval	2	1	0	0
No therapy	7	0	0	1

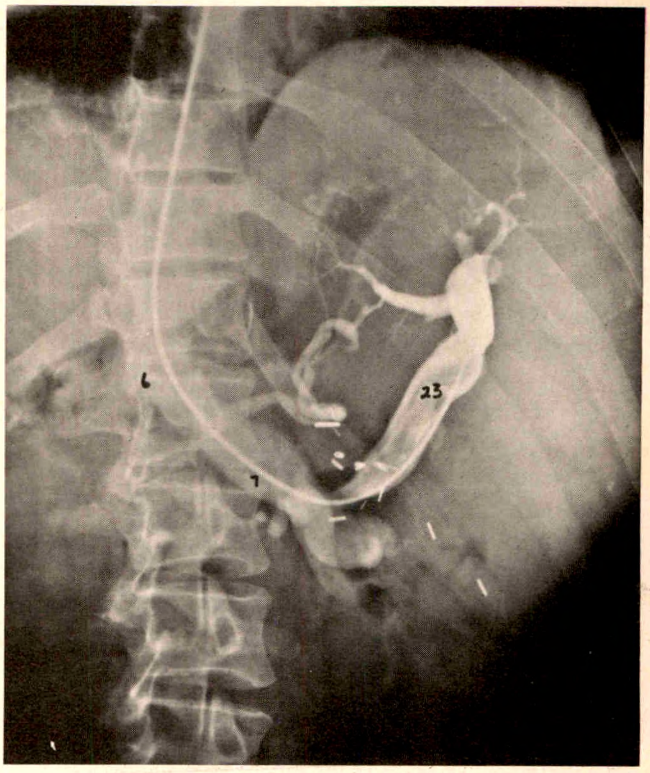

FIG. 2. Stenosis of a DSRS 4 months after operation in a patient who had phlebitis of the splenic vein.

Portal perfusion of the liver. Portal perfusion of the liver *via* the portal venous collaterals was present in all patients immediately after operation. In 15 patients restudied from 6 months to 6 years later, this hepatic portal perfusion was sustained in every instance (Figs. 4 and 5), and bleeding controlled (Fig. 6). Proof of portal perfusion requires repeat superior mesenteric angiography in PVT patients.

Rebleeding. There have been three episodes of bleeding after operations. Two of these were in the early postoperative period, a phenomenon seen frequently in selective shunts. This was managed by revision of a kinked shunt in one patient, and by sclerosis in the other following documentation of shunt patency by catheterization. One patient bled at 1 year after a gastroepiploic shunt, which had required dilatation for stenosis. After the bleeding episode, a reoperation with reanastomosis was done successfully. The patient with a thrombosed splenocaval shunt has not rebled.

Encephalopathy. There has been no evidence of encephalopathy clinically, by EEG, or by trail testing thus far. However, the post-shunt period is still short, with the first patient just 10 years post-shunt.

Study group. The quantitative data on the six patients studied serially in depth is summarized in Table 5 and Figures 7 and 8. There is no significant change in GEC, liver volume, and portal perfusion. Liver blood flow shows a significant ($p < 0.05$) increase at late follow-up. Spleen volume, shown in Figure 7, shows a significant reduction ($p < 0.05$) from the preoperative mean (±SD) of 905 ± 540 cc to 472 ± 246 cc at 1 year and 337 ± 169

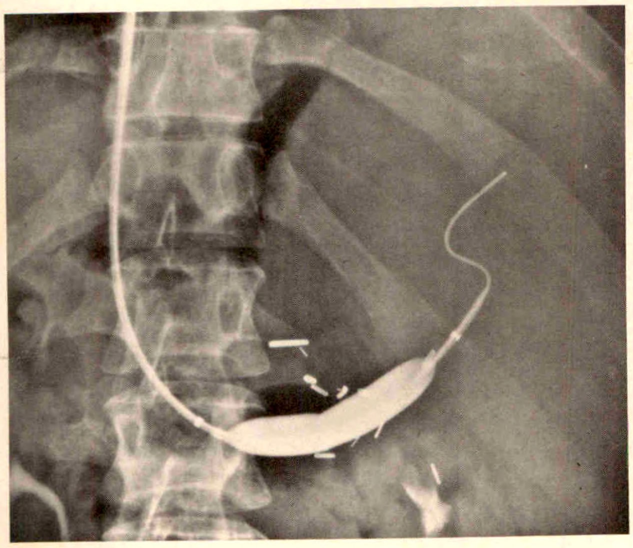

FIG. 3. Dilation of the stenosis was satisfactorily achieved with the balloon, shown in position across the splenorenal anastomosis.

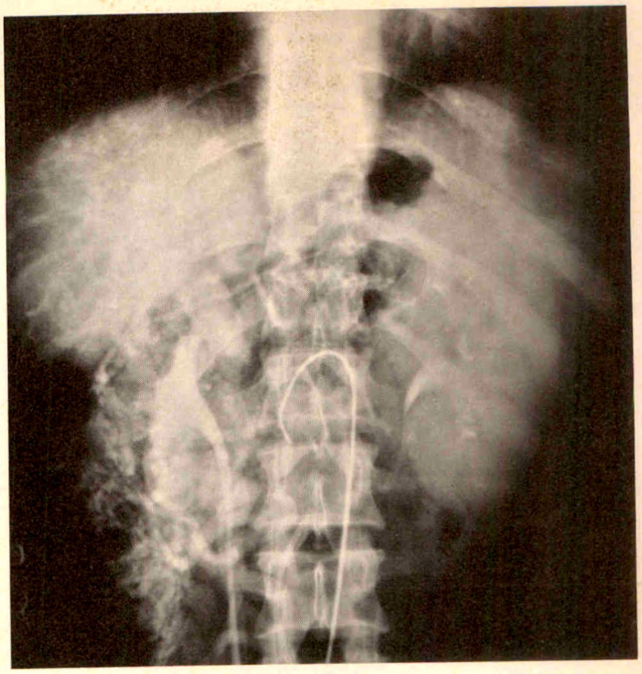

FIG. 4. Portal perfusion in portal vein thrombosis (preoperative). Venous phase of superior mesenteric artery injection showing cavernous transformation and excellent filling of all intrahepatic portal venous radicles.

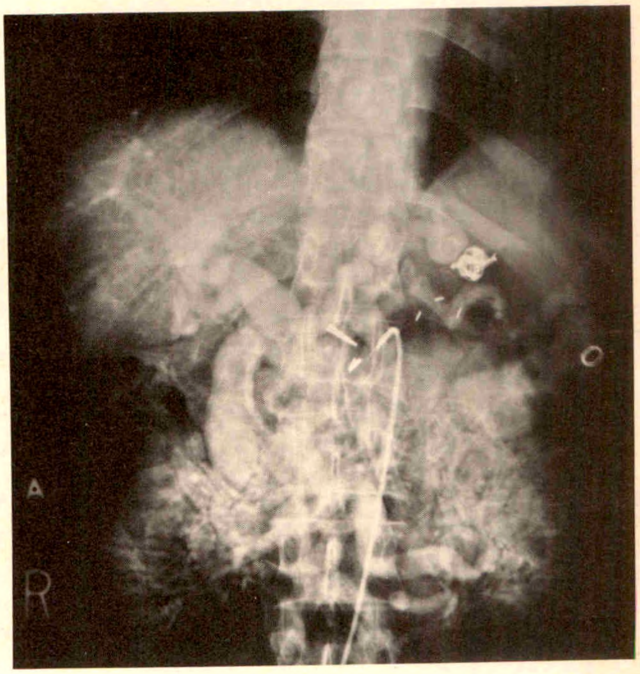

FIG. 5. The same study in the same patient 6 years after DSRS. Excellent portal perfusion is shown; the large hepatopetal collaterals are evident.

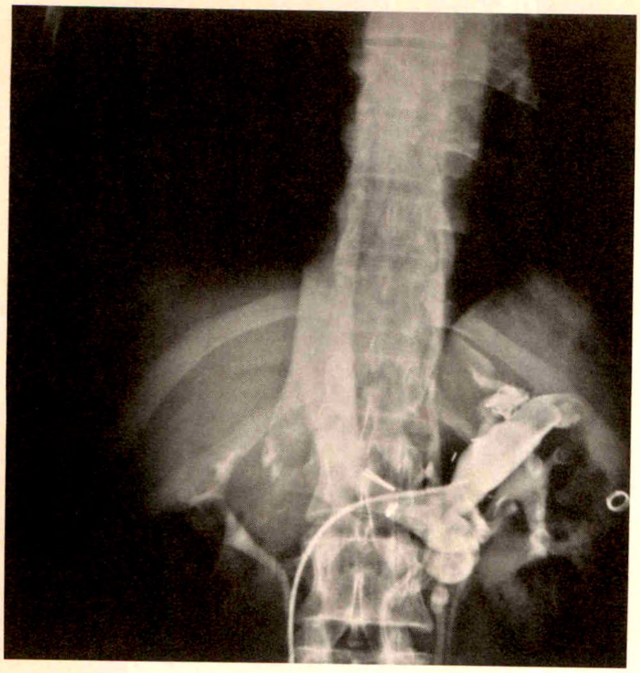

FIG. 6. Widely patent shunt at 6 years in same patient as Figures 4 and 5.

cc at mean 4.5 year follow-up. Platelet count increase, shown in Figure 8, is also significant ($p < 0.05$), rising from 99 ± 59 to 145 ± 46 and 183 ± 35 K/mm^2 at 1 and 4.5 years, respectively.

In addition, three patients in this group have had successful and uncomplicated pregnancies in the past 3 years. This is a further measure of return to normality after DSRS.

Other shunts. In two patients with prior splenectomy, a superior mesenteric caval shunt was possible. A Marion–Clatworthy vein-to-vein anastomosis was done in a patient who had rebled repeatedly after a splenectomy at age 15 years. At the time of shunting the patient was 56 years old and had received more than 100 units of blood over the post-splenectomy period. After shunting there has been no rebleeding and the shunt has been shown to be patent by angiography at 16 years. The patient has no clinical, psychometric, or EEG evidence of encephalopathy. She has had a mild hyperammonemia in recent years; the liver volume is 990 cc.

TABLE 5. *Data on Hepatic Function and Hemodynamics in 6 Patients Studied In Depth Before and Serially After DSRS*

DSRS (N = 6)	Before	1 Year	3–6 Years
GEC (mg/min)	392 ± 40	377 ± 66	403 ± 66
LBF (ml/min)	1069 ± 345	1078 ± 345	1500 ± 429*
Portal perfusion	1	1	1
Liver volume (cc)	1039 ± 242	1131 ± 195	1159 ± 169

* $p < 0.05$.

A second mesocaval shunt used a dacron interposition graft. This patient did well for 7 years and then rebled. Angiography revealed an occluded shunt; current therapy is endoscopic sclerosis.

Four makeshift shunts were constructed using large but variceal vessels, all of which thrombosed. These patients are being managed currently by sclerotherapy.

Central splenorenal shunt with incapacitating encephalopathy: closure of shunt. The patient had a central splenorenal shunt performed at age 21 years, developed hyperammonemia 15 years later, followed by progressive hepatic encephalopathy. When first seen at Emory (age 42 years), there was overt and severe symptomatology despite a rigorous antiencephalopathy regimen. Blood ammonia level after a meal with 20 g of protein exceeded 500 µg/dl. The patient was totally incapacitated. A decision was made to close the shunt and manage future bleeding, if necessary, with sclerotherapy. After closure of the shunt, clinical and laboratory abnormalities began to clear rapidly. Within a short time she could tolerate a normal protein diet. Of equal significance was the return to normal of the EEG, memory, and other aspects of CNS function, demonstrating the reversibility, by restoration of portal perfusion, of a most severe encephalopathy sustained for a period of years.

Five years later, having enjoyed excellent health and return to all her normal activities, variceal bleeding recurred. Endoscopic sclerotherapy was offered in her home city; she and her family elected to return to Emory. While awaiting urgent air transportation to the United States and Atlanta, the patient sustained an exsanguinating hemorrhage and died.

Non-shunt Operations

Before the rediscovery of endoscopic sclerotherapy, nonshunt procedures such as splenectomy and gastric devascularization were often used in patients for whom no shunt was possible or had been attempted and failed. Twenty patients fall into this category, 12 of whom had the spleen *in situ* at the time of operation at Emory. This group has not fared well with rebleeding occurring in more than 50%, a mortality rate of 25%, and an additional four patients were lost to follow-up. The severity of mortality and morbidity raise the question of the appropriateness of procedures using splenectomy without a shunt for patients with PVT.

Simple devascularization of the stomach may be useful, on occasion, essentially to improve effectiveness of long-term endoscopic sclerotherapy. There was one spectacular success in the devascularization group,

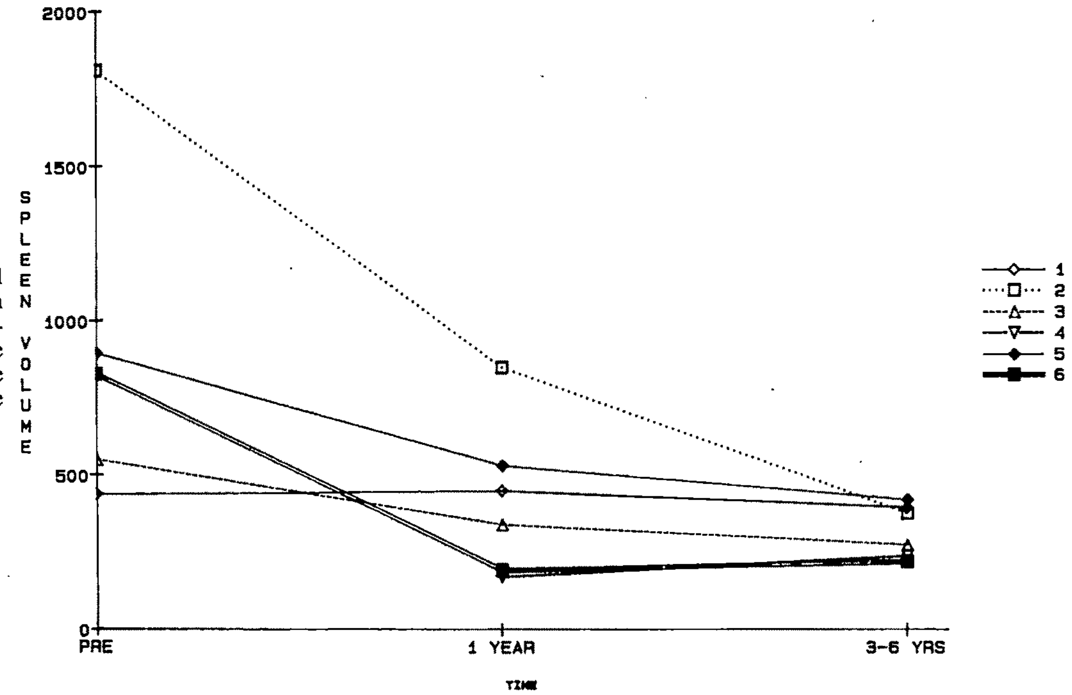

FIG. 7. The individual changes in spleen volume in the 6 patients studied in detail after DSRS. The changes from preoperative to 1 year and 3-6 years are statistically significant.

which highlights a principle and emphasizes an exception to the rule. The patient was referred with massive gastrointestinal (GI) bleeding that was emanating from below the duodenum. This man had sustained a common bile duct injury for which a Roux-en-Y loop of jejunum was used in the repair. With the occurrence of hemorrhage, an angiogram was obtained that disclosed PVT and a large collateral from the susperior mesenteric vein to the area of the hilus of the liver. At operation the Roux loop was greatly distended with blood. The bowel was opened near the biliary–enteric anastomosis and torrential bleeding was coming from varices passing from the jejunal loop into and up the common bile duct. A ligature of the jejunal branch of the superior mesen-

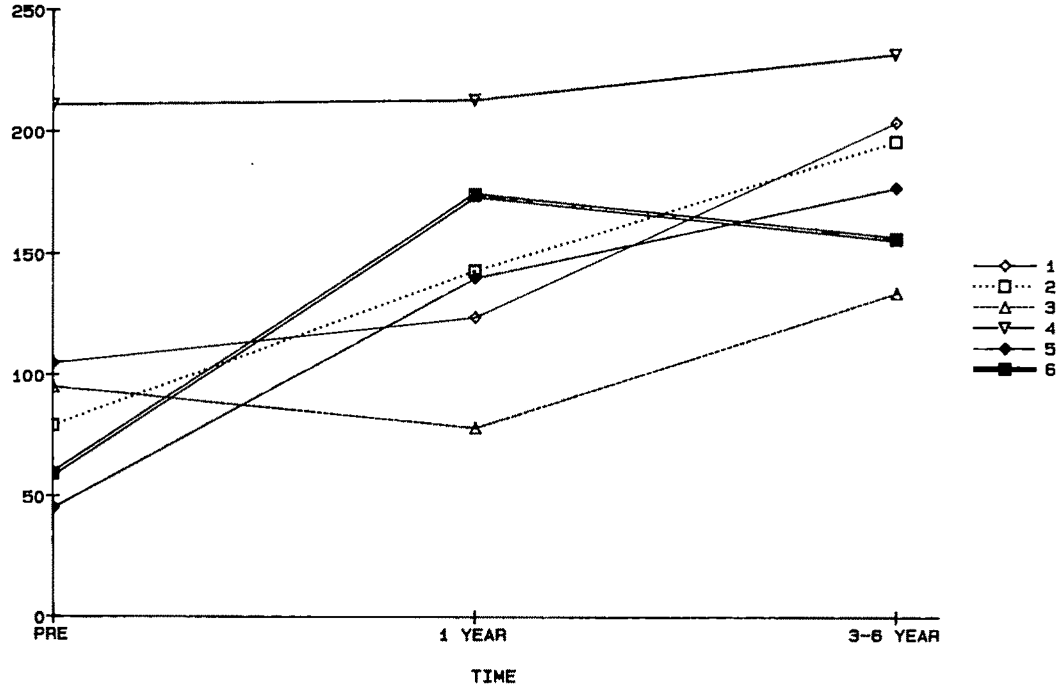

FIG. 8. The individual changes in platelet counts in the six patients serially studied after DSRS. Note the initial thrombocytopenia in 5, and the continuing and significant improvement.

TABLE 6. *Outcome for Patients with no Patent Major Portal Vein Tributary at Time of Referral*

Management	No. of Patients	Rebleeding	Deaths
Splenectomy	10	6	2
Devascularization/sclerosis	10	5	3
Sclerosis	12	4	0
Makeshift shunt	4	3	0

teric vein at its base in the mesentery caused immediate cessation of bleeding.

The principle of hepatopetal collaterals in PVT is demonstrated clearly by this patient, and secondly illustrates the need to be aware of unusual sources of bleeding into the GI tract. Another instance of the Roux-en-Y–PVT connection has been reported by the Emory Faculty from Grady Hospital.[21] A Roux-en-Y loop provides a major conduit for inflow into the collateral veins perfusing the liver.

Endoscopic Sclerotherapy (EVS)

EVS has become the initial form of therapy for bleeding esophageal varices in the cirrhotic patient in many centers. In PVT, however, the pathophysiology of the process is different and hard data as to outcome are scarce. One of our concerns has been the danger of leading to further phlebitis and/or thrombosis of the major venous tributaries that could be used for a selective shunt. However, based on long-term studies of other therapies in PVT, we believe it is too early to take a firm position as to the proper role of EVS and PVT patients. There are no good data with long-term follow-up to answer the questions of rebleeding rate, extension of thrombosis, and other forms of morbidity and mortality of which we are aware. Repeated studies have small numbers with limited follow-up.[14-17] In the Emory series, 29 patients have had sclerotherapy for long-term management. Twelve (41%) have had EVS begun here after splenectomy elsewhere or having no patent major tributaries of the portal system. The remaining 17 followed operation here, including six unsuccessful shunts (1 DSRS, 4 makeshift, 1 mesocaval).

The first patient with PVT sclerosed at Emory was in 1978 and has a 9-year follow-up; the mean duration of follow-up is 50 months. Rebleeding has occurred thus far in eight patients (28%), but there has been no mortality. Morbidity has included one patient with aspiration pneumonia and two patients with long-term neurological sequelae in whom cause and effect has not been clearly shown. Although the precise role of EVS remains to be defined, it has already proven to be a valuable addition to the therapeutic armamentarium.

Discussion

There remain several areas of debate regarding the proper role of various diagnostic and therapeutic modalities in patients with PVT who have experienced GI bleeding. The issues range from the natural history of the disease, if left untreated, to results and complications of standard operative procedures, to new and promising forms of nonoperative interventional therapy.

Natural History

This study cannot assess this issue as all patients were referred by other physicians. There is no primary pediatric or family practice program at the Emory Hospital and consequently we rarely see patients with asymptomatic PVT.

Results of Operative Therapy for Bleeding Varices

In this aspect of the disease the Emory program has been quite active. Since 1971, the year our ongoing program for the study of portal hypertension was begun, we have seen 70 patients with PVT and a history of bleeding varices or other symptoms. Over half of our patients had had one or more operative attempts at control of varices before first being seen at Emory. This patient population (those with prior operation) has led to heightened understanding of two fundamental issues. First is the poor long-term results achieved in patients in whom no major tributary of the portal system was patent, and second, the predominant role splenectomy has played in producing this unhappy result. Table 6 shows the disheartening figures for those patients with no patent vessel for possible shunt; the poor results for long-term control of bleeding probably carry over into the sclerotherapy group as well. Although we do not have good data on the patency of the portal system before splenectomy in other hospitals, some insight can be obtained by comparing the success of shunt operations at Emory in patients with the spleen present *versus* those in whom it had been excised. After the initiation of the selective shunt policy at Emory, we have seen 30 patients in whom the spleen was present at operation and a shunt was possible in 25 (83%). In stark contrast is the 3 of 37 (8%) success rate for those with any prior operation and the 2 of 24 (8%), which followed simple splenectomy. Our dismay at these figures is intensified by the realization that many of the splenectomies were done solely to relieve the thrombocytopenia of hypersplenism.

Patency of Shunts

Long-term patency of shunts in patients with PVT is considered a rarity by some authors, but was clearly achieved in this study. Of the 25 patients whose vessel status permitted construction of a selective shunt, 24 (96%) had patent shunts proven by angiography before discharge. One patient had a minor revision of a kinked but open shunt; the sole occlusion was in a splenocaval anastomosis. The first DSRS patient is now 10 years post-shunt and has a patent shunt.

Because of the phlebitis present in many of the veins used for shunting, early reassessment has been carried out. In six of the 24 patent selective shunts, nonoperative dilatation was required for stenosis at the 3- or 6-month evaluation. One gastroepiploic anastomosis failed dilatation and required revision of the anastomosis at 1 year.

All of our four makeshift shunts in this series have occluded, four of five central splenorenal shunts done before referral to us had occluded, and one of two mesocaval shunts (an interposition graft) occluded. These results certainly are influenced by the nature of the phlebitic veins often encountered and the altered anatomy between tributaries must also be important. A central splenorenal shunt when the superior mesenteric and portal veins are thrombosed and the spleen is excised as part of the operative technique would certainly carry a high risk of failure! The DSRS maintains the high volume splenic flow as well as the collateral flow; this is undoubtedly a major factor in the excellent patency rates demonstrated by this study.

Control of Bleeding

Again, the selective shunts have been excellent in this regard. There has been a single long-term rebleed, in a patient with a stenosed gastroepiploic–renal shunt. There were two early postoperative bleeding episodes, a feature of selective shunts where transplenic decompression may require several weeks for maximum pressure reduction. Such bleeding is common before leaving the hospital; subsequent rebleeding has not occurred in either patient.

Nonshunting operations are performed widely in countries with portal hypertension secondary to schistosomiasis, hepatic fibrosis, and nonalcoholic cirrhosis, but numerous authors have cited the many dangers of splenectomy in the PVT patient.[4,9,12] The functional anatomy of the portal system is radically altered by the thrombotic process and splenectomy can accentuate this dysfunction. This may take many forms, such as thrombocytosis, venous infarction of the bowel, increased susceptibility to infection, loss of opportunity for a selective shunt, or by simply increasing the likelihood of esophagogastric bleeding by removal of low risk collaterals. As one reviews these patients and the analysis of experts in the field of PVT, the negative impact of splenectomy (with or without gastric devascularization) appears undeniable. There are no controlled trials of this question and there should be none with the possible exception of patients with an intact spleen but occluded splenic vein who have failed sclerotherapy.

Encephalopathy

The question of portasystemic encephalopathy in PVT, with or without shunts, continues to stimulate workers in this field.[22–24] There have been a number of reports indicating the problem to be significant[1,22,23] and others that fail to find real encephalopathy in any of their patients.[8,24]

The patient re-reported here is undeniable evidence that the syndrome of nitrogen-dependent encephalopathy in its severest form can occur after a total shunt in a patient with PVT. The question now is how often does this occur and should it enter into the decision as to optimal therapy for individual patients. There are insufficient data at this time to make a definitive statement. For accurate assessment of this question, studies are needed related to the pathophysiology of the encephalophy itself and two additional prerequisites. First is the long-term study of such patients (15–25 years) and second is the demonstration of a patent shunt at the time of restudy. Some recent studies from France illustrate these points.[24] Although only minor abnormalities were reported in those patients, it should be noted that the mean interval after operation was less than 5 years, and shunt patency was not documented. Crucial to this field will be long-term studies with clear demonstration of shunt and portal perfusion data at the time of the late assessment.

In our data on the selective shunt approach we have shown patent shunts and low rebleeding rates, sustained portal perfusion of the liver, and lack of encephalopathy; however, the time frame is too short (longest follow-up 10 years) for a definitive conclusion.

Sclerotherapy

An assessment of this new therapy is difficult at this time. There is little doubt that EVS is a major therapeutic modality for control of variceal bleeding, and the only question being when it should be used. The rebleeding rate for this group has not yet been determined. Rebleeding in the Emory patients has occurred eight times (28%), but this includes a large number of patients who had had previous operation which proved to be unsuccessful. The results of sclerotherapy as the first intervention has not been firmly established, in part because of the relatively recent return to this therapeutic modality. Small series[15–17] or incomplete[14] and limited follow-up leave this question open. A concern at our institution is the possibility of the sclerotherapy leading to occlusion of veins that could be used for a definitive shunt. Although there have been anecdotal reports of thrombus propagating to the intra-abdominal vessels, a true evaluation of this risk has not been accomplished. Sclerotherapy for varices in cirrhosis, chronic active hepatitis, and hepatic fibrosis has yielded good results at Emory; extension of this judgment to the PVT patients would be premature.

Miscellaneous Aspects of Interest

Eleven of the 25 DSRS patients are women in the childbearing age and thus far three have become pregnant. All three had uneventful deliveries of normal babies. With similar results from other centers there should be little concern about childbearing if such is desired by the patient.

Coagulopathy was not routinely studied but two patients are known to have an hypercoagulable syndrome. One has protein C deficiency and the other has an antithrombin III deficiency. PVT patients should be studied routinely for problems related to hypercoagulability and long-term anticoagulant therapy used when indicated.

The Roux loop anastomosed to the common bile duct provided graphic demonstration of the volume of portal flow which can perfuse the liver around a thrombosed portal vein. This phenomenon is not seen in portal sclerosis (ideopathic portal hypertension), another condition in which a normal liver biopsy and normal liver function are common. The venous pathology in portal sclerosis is so peripheral that no venous pathway can bypass the obstruction. In that regard portal sclerosis resembles schistosomiasis; there are hepatofugal collaterals, but no hepatopetal portal collateralization. Simple cholecystectomy in a PVT patient can be a vivid experience because of the collateral flow through and around the gallbladder bed!

Recommendations

This experience has led us to evolve our current management as shown in Figure 1. The emphasis is on full evaluation to determine the optimum method to prevent further bleeding. In essence, if a patent splenic vein can be found, a DSRS is, we believe, optimum therapy. In those who have no vein suitable for selective variceal decompression, sclerotherapy probably offers the best alternative approach.

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DISCUSSION

DR. JOSEF E. FISCHER (Cincinnati, Ohio): This excellent presentation is another logical step in the attempt of the Atlanta group to define the place of shunting in the therapy of these difficult patients. As they very well pointed out, the patient with extrahepatic portal block has a basically normal liver and, unlike the patient with cirrhosis, has a dual blood supply to the hepatic lobule, the anatomy of which is normal.

There is no better theoretical place than in the patient with extrahepatic portal block for the idea of dividing the left side and the right side of the portal circulation in order to sustain perfusion to the liver. Total perfusion to the liver is probably decreased because, as the fourth power of the radius and the collaterals tend to be small, flow varies; but, in fact, as they pointed out, hepatic resistance is normal.

I would like to ask three questions of the group. First, Dr. Warren and his group have for some time attempted to define portal blood flow and separate the components of hepatic artery and portal venous flow, and I wonder whether they have any data through which they have been able to estimate the respective contributions of the hepatic artery and what residual portal venous flow exists in this particular population.

The contribution of the portal venous flow probably has some long-term prognostic significance.

Secondly, I gather that you do not recommend prophylactic shunting in this group. Prophylactic shunts are generally thought not to be indicated in patients with large varices and who have not bled; but in view of the fact that these patients who have not bled represent a group of patients with relatively normal preserved flow, in a patient with hypersplenism that is symptomatic and worries the gastroenterologist, would you allow yourself to be talked into a prophylactic "distal splenorenal shunt"?

I have on a couple of occasions. I have not yet been sorry, and I wonder what your own experience has been.

The third question was partially answered, but if memory serves me correctly, in 1964, Thompson and Sherlock in the *Lancet*[1] reviewed a very extensive long-term experience with extrahepatic portal block, coining the term "premature aging of the liver"—a condition in which patients with extrahepatic portal block seem to show a terminal phase of their extrahepatic portal block that is indistinguishable from that of patients with cirrhosis; and these patients died of encephalopathy, hepatic failure, ascites, and jaundice, at the age of approximately 50 years.

The argument was used in that paper that long-term deprivation of the normal volume of portal flow was responsible for hepatic failure. Is there another patient population that you have not discussed in this paper, or are these patients not old enough to exhibit this hepatic failure, or do you simply not believe in the entire concept?

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DR. JOAQUIN S. ALDRETE (Birmingham, Alabama): That is a very nice updating of an old problem by Drs. Henderson, Millikan, and Warren.

I think that, in some of these patients with extrahepatic portal vein thrombosis, an important etiological factor, in at least one group, is hypercoagulability, which can usually be documented before operation, when the platelet count is over 300,000.

It is important to note that most of these patients have not only thrombosis of the portal vein itself, but also have some intraluminal trabeculations that extend toward the splenic vein and superior mesenteric veins. These trabeculations are part of the intima and cannot be removed; thus, eventually they lead to thrombosis of these veins.

The patients who do not have this extensive involvement and in whom the splenic vein is clear are suitable for a distal splenorenal shunt. My first question to Dr. Henderson is: Did you study some of the coagulation parameters in these patients before operation?

Because these patients have relatively normal liver function and their ascites can be effectively treated, they can be well for a long period of time. You showed in your slide where you categorized the patients studied in groups, according to the therapy they received. There were seven patients that received no therapy, and theirs was the only group that didn't experience any rebleeding. Would you give us some more information on that group?

Dr. Henderson, you mentioned a patient that had a central splenorenal shunt and developed encephalopathy, and later on, you showed that there was flow through the portal vein. I am unclear. I thought that all these patients had thrombosis of the portal vein. Did this patient re-establish the flow through other collaterals communicating with the intrahepatic portal branches? We have seen this once or twice; nevertheless, would you clarify that for me?

This paper is very important because it categorizes the indications for operation in each one of the groups of patients with extrahepatic portal thrombosis.

DR. MARTIN A. ADSON (Rochester, Minnesota): This study is just elegant: the long observation of a carefully studied group of patients. I have a single question. This concerns a patient about 25 years old with a distal splenorenal shunt done about 10 years ago. He is doing very well, playing racquetball, going into postgraduate training. He has had splenic infarcts on two occasions. These were not incapacitating, but enough to worry me about what is going on. No obvious coagulopathy is evident.

Can the authors tell me what I should think about that patient? Can I do something to prevent further troubles along those lines?

DR. ROBERT ZEPPA (Miami, Florida): The authors are indeed to be congratulated on this study, since it is one of the largest surgical studies of portal vein thrombosis with which I am familiar, and because no other patients have been studied quite so effectively and thoroughly as this group.

We had a small experience with this particular problem, but in no way does it compare to the particular series that has been reported today.

I have just one question. Except in cirrhotic patients, our experience with spontaneous thrombosis of the portal vein and extrahepatic portal system is very, very limited.

Our experience with portal vein thrombosis has been almost totally restricted to those patients who have had a history of omphalitis at birth, or severe peritoneal sepsis, either during childhood or young adulthood, with complete thrombosis presumably from pyelophlebitis.

These patients, interestingly enough, have done fairly well after devascularization procedures where no shunt could be done. This is not to say that the devascularization procedures in our hands eliminates the varices. The varices are still there, but the bleeding rate has been strikingly low, which has surprised us no end; and so far very few of these patients have had to come to sclerotherapy.

I wonder if the authors would comment upon the etiology of the thrombosis in their series of patients.

DR. W. DEAN WARREN (Closing discussion): This is sort of a complex topic and not of interest to a lot of you here in the audience, but an understanding of this disease will help a fairly large number of patients.

Joe Fischer, a long-time worker in the field, has raised some very pertinent questions. The first regards the quantitation of portal flow. He always likes to use that question because he knows that I can't answer it, and it gives him a perverse sense of pleasure, as you can see by his laughter. We utilized a technique at one time measuring radionuclide fractions in which it was estimated that about 30 to 40% of normal portal flow reached the liver through the huge collaterals that are called "cavernous transformation" by angiographers.

We do not advocate prophylactic shunt in these patients, but like you, have on a couple of occasions yielded to pressure from patients who live far from Atlanta, have a huge spleen, a platelet count of 50,000, and a white count of 1800; the doctor says, basically, "Well, I will just have to get his spleen taken out up here." We then say, "All right, it is better to do the shunt." A shunt takes care of the splenomegaly and hypersplenism; we don't advocate prophylactic shunt, and do it only when we are locked in.

Sheila Sherlock has mentioned this hepatic failure or fatigue syndrome that comes on after many years. I don't think it is explainable from our data. It seems to occur in about 10% of patients. You always wonder about viremias from the many, many transfusions these patients have had. The adult population with which we deal usually has had many transfusions; one patient had over 200 units of blood transfused prior to her shunt. We simply can't predict what will happen farther down the line, but we will be following these patients very closely. Dr. Fischer, yours is a very good question.

Dr. Aldrete, we do study these patients for hypercoagulability, and this is another good question. We have never seen the thrombocytosis to which you refer preop, except when there has been a splenectomy. If there is hypersplenism with thrombocytopenia and you take the spleen out, then there will be thrombocytosis in a certain number of patients, and we have had one patient in whom it then proceeded to cause coagulation of the entire portal system. It is a real problem.

We have also found deficiencies in protein C and protein S, which can give a diffuse hypercoagulability; unless the patients have bled, we have not operated on such patients, because they are a fairly marked increased risk. In that group of patients who have not had an operation and undergone sclerotherapy, careful long-term follow-up is very important. They are going to continue to be subject to bleeding, because their stomach will have sustained portal hypertensive pressure.

In terms of flow, PVT is a very important subset. Those big collaterals that Dr. Henderson showed in his slides are not hepatofugal collaterals. They are hepatopetal collaterals, carrying portal blood to the liver; this is what differentiates this condition from cirrhosis. In PVT, the liver has a normal sinusoidal pressure, as does the spleen after shunt. The collaterals go to the liver, therefore, as well as the spleen. In post-shunt cirrhosis there is high pressure in the liver and low pressure in the spleen, this gradient tends to push portal flow toward the spleen over the course of the years, and that is an important differential for the long-term well-being of these patients.

Dr. Adson has had a large experience in this field. As to the patient that he presents with the intrasplenic infarct, I have no experience. Some of these people do have a definable coagulopathy; I think I would get a hematological consult to see if there isn't a syndrome in which portal vein thrombosis might be a component of a larger problem of a hematologic nature.

Dr. Zeppa, my old-time friend and colleague, mentioned omphalitis and sepsis. We can identify such patients less often because ours are almost all adults. We don't see the children that you and others with children's hospitals do, but Sherlock estimated that about a third of them could be proven to come from one of those two causes. The new syndromes of the coagulation abnormalities are going to account for some more. We don't do quite the blue stomach devascularization of Zeppa and Womack and Johnson, but rely more heavily on a sort of devascularization, and then follow that with sclerotherapy.

Biliary Secretory IgA Levels in Rats with Protein–Calorie Malnutrition

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Malnutrition is a recognized cause of failure of host defense mechanisms. In the past 5 years, it has been demonstrated that the gut, long known to have significant morphologic changes with protein calorie malnutrition (PCM), is an immune organ affected by malnutrition. To assess the role of biliary immunoglobulin A (S-IgA), part of the barrier to bacterial invasion from the gastrointestinal tract, the following study was performed. Seventy-eight Fisher female inbred rats weighing 110–130 g were randomly separated into two groups. The control rats were fed standard rat chow. The experimental rats were fed a 2% agar protein depletion (PCM) diet (USP XV). The biliary tract of the rat was cannulated with Silastic tubing and bile flow and rat secretory immunoglobulin A (S-IgA) was sampled at intervals. S-IgA was measured by the Elisa method. Total bile protein was measured by micro-Kjeldahl. Bile was collected from the rats on day 0, 7, 14, 21, 29, 36, 42, and 49. During the study, the weight of rats fed the PCM diet decreased from 127.4 ± 14.5 g at day 0 to 83 ± 2.6 g on day 37. Control rats gained weight from 124.4 ± 14.5 g at day 0 to 153.6 ± 3.8 g at day 37. Total biliary protein at day 0 was 2.52 ± .05 mg/ml and at day 36 was 2.51 ± 11 mg/ml for PCM rats and 2.57 ± 10 mg/ml for control rats. Normal rats and control rats both had an initial increase of S-IgA from 2.74 ± 73 mg/ml on day 0 to 5.75 ± 1.75 mg/ml on day 37. Both PCM and control rats demonstrated an increase in S-IgA levels despite significant loss of weight in the experimental group. Similarly, total biliary protein was not decreased in either group. The results suggest that gut immune system is preserved despite significant protein calorie malnutrition.

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INFECTIONS ARE STILL THE MAJOR CAUSE of morbidity and mortality in our society.[1] Most of these infections occur after initial exposure of foreign proteins, bacteria, or viruses to mucous membranes. In response to the continual threat of infection, the body has developed an efficient host immune defense system concentrated in the mucous membranes. In the intestinal tract, because of the continous exposure to microbes and food antigens, it has been estimated that there are about 7.5 (10^{10}) anti-body-producing cells lining the mucosa of the gastrointestinal tract. Heremans calculated that this represents approximately 50 g of immunoglobulin-producing cells in the gut, which is comparable to the mass of the immunoglobulin-producing cells in the spleen.[1]

Although immunoglobulin A (IgA) had been observed as a precipitate in immunoelectrophoresis of human serum,[1] its purification allowed its role to be defined. IgA was also found to be the predominate immunoglobulin in human milk and human saliva as well as in many other secretions.[2] Tomasi demonstrated that secretory IgA was a dimer of IgA molecules with an additional polypeptide chain, the secretory component (SC).[3] It was later discovered that S-IgA also contained another polypeptide structure called the J-chain. The J-chain adds to the compact structure of S-IgA, and thus S-IgA antibodies are more resistant to enzymatic action than are serum IgA antibodies.

IgA with the J-chain is produced by specialized lymphoid cells (B-cells). It is then linked to SC on the surface of specialized epithelial cells (M-cells).[1] According to Brandtzaeg, the binding of Sc to the IgA dimer requires the presence of the J-chain.[4] After the binding of the IgA dimer to the SC polypeptide, the complex is transported through the epithelial cell and is then released at the apical surface of the cell. Thus, S-IgA is found in secretions like milk, saliva, tears, bile, as well as in fluids of the nasal, bronchial, intestinal, and genitourinary surfaces. The levels of IgA are indirectly regulated by the amount of exposure of foreign antigen.

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According to Walker and Isselbacher, diminished levels of S-IgA may be related to mucosal atrophy.[5] Patients with S-IgA deficiency have an increased incidence of circulating antibodies to food and bacterial antigens, which suggests an increased permeability of the mucosal barrier. Patients with protein–calorie malnutrition may have an increased incidence of intestinal infections, circulating antibodies to food and bacteria, and higher incidence of autoimmune disease.

Malnutrition affects the humoral immune system in many ways. The B lymphocyte subpopulations and immunoglobulin synthesis of serum IgG, IgM, and IgA are usually normal or increased; however, secretory IgA (S-IgA) levels in the respiratory and gastrointestinal fluids are generally decreased as are secretory IgA antibody responses.[6]

Secretory IgA binds and neutralizes viruses and bacterial enterotoxins, S-IgA agglutinates bacteria and prevents the attachment of bacteria to epithelial cells. However, the bacteriolytic action of S-IgA antibodies *via* lysozyme and the complement system has been verified by some investigations and not by others. Successful immunization for poliomyelitis involves the complex gut immune system. The polio virus (Sabin) oral immunization has led to a predominately IgA response in intestinal secretions, whereas parenteral immunization (Salk) did not cause elaboration of intestinal antibody.[7] The local immune response is dependent on route of administration (oral or parenteral) as well as the amount of antigens. Secretory IgA is the predominant antibody in bile. Polymeric IgA is transported into bile after the addition of the SC portion by the hepatic cells[1] and is a major source of intestinal S-IgA.

From previous work, it has been demonstrated that malnourished patients exhibit an increased susceptibility to infection, and thus, one might expect a decrease in the amount of S-IgA.[8] Protein–calorie malnutrition has a profound effect on the structure of the gastrointestinal (GI) tract. Moreover, atrophy of mucosal epothelium, Peyer's patches, and gut-associated lymphatic tissue (GALT) could diminish the cell numbers and function for maintaining GI immune function, specifically S-IgA.

Moreover, earlier studies have shown that route of nutrition (parenteral or enteral) influences gut morphology. Gut atrophy occurs when food is absent from the GI tract and is associated with increased susceptibility to infection.[9,10] Acknowledging that S-IgA is only one component of the complex GI immune system, these studies were done to determine if S-IgA was affected by malnutrition in rats. Because S-IgA is prominent in bile, the model used evaluates S-IgA in bile.

Materials and Methods

Seventy-eight female inbred Fisher rats weighing 110–130 g were randomly separated into two groups of 38 and 40. The control group included 38 rats, the test (PCM) group included 40 rats. The control rats were fed a standard rat chow diet and water *ad libitum*. The PCM rats were fed a 2% agar protein depletion diet (USP XV) and water *ad libitum*. This diet was selected as the test rats will lose a predictable amount of weight. Moreover, few rats will die because of malnutrition.

During the experimental period, five rats from each group were studied every 7 days. The rats were weighed and anesthetized intraperitoneally with sodium pentathol, 0.01 ml/100 g body weight (BW), and intramuscularly with ketamine, 0.01 ml/100 g BW. A celiotomy was performed and the common bile duct was cannulated with Silastic tubing (O.D. 0.025″, I.D. 0.012″). Bile was collected over a 30-minute period and the rats were killed.

The rat bile specimens were then measured and the bile flow rate was calculated. It is important to measure bile flow so that obstruction of the bile flow by cannulation can be avoided. The samples were stored in plastic vials at −20 C until the total protein and S-IgA assays were performed (Fig. 1).

Rat S-IgA used for standards in the assay was purified from rat bile courtesy of the Rosalind Russell Laboratory at the University of California–San Francisco. Standards were prepared by diluting rat S-IgA with 0.01 M PBS— 0.1% Tween 20 pH 7.4 at concentrations of 12.5–200 mg/ml on the day the assay was performed.

Immulon II 96-well microtitre plates (Dynatech Labs, Alexandria, VA) were coated with goat anti-rat S-IgA (1 μg/ml in 0.01 M PBS pH 7.4, 200 μl/well). The goat antisera was purchased from Miles Laboratories (Ames Division, Elkhart, IN) and purified. The purification of the antisera involved dialysis with 0.02 Tris-HCL. 0.028 M NaCl buffer pH 7.2, purification of the IgG fraction *via* affinity chromatography with DEAE Affigel blue (Bio Rad Labs, Rockville, NY), concentration with Lyphogel (Gelman Sciences, Inc., Ann Arbor, MI), dialysis with 0.01 M phosphate buffered saline (PBS) pH 7.4, and stored at 4 C in a borosilicate glass vial. The optical density at 280 mm of the antisera was used to calculate the protein concentration. Plates containing the goat anti-rat S-IgA were placed in a 37 C humid incubator for 1–2 hours, then stored at −20 C. Before being used, the plates were thawed and washed three times with PBS-Tween 20, allowing 2–3 minutes equilibrium time per wash, then drained and blotted. Bile samples were thawed and diluted 1:20,000 with PBS-Tween 20. Two hundred microliters per well of blank solution (PBS-Tween) was pipetted to the first two columns of a coated microtitre plate. To avoid the "edge effect," the edge rows were not used, and 200 μl/well of various concentrations of standard was pipetted into two rows of the plate. Adjacent wells were filled with 200 μl/well of PBS-Tween 20 and the remaining wells received diluted

TABLE 1. *Biliary Flow, IgA Values—Normal* Versus *Control*

	Control (N = 5)			Protein Calorie Malnutrition (N = 5)		
Day	Flow (ml/hr)	Total Protein (mg/ml)	S-IgA (mg/ml)	Flow (ml/hr)	Total Protein (mg/ml)	S-IgA (mg/ml)
0	1.42 ± 0.59	2.52 ± 0.05	2.74 ± 0.73			
7	1.54 ± 0.58	2.61 ± 0.10	1.68 ± 0.77	1.44 ± 0.49	2.40 ± 0.07	1.95 ± 0.54
14	1.62 ± 0.16	2.55 ± 0.05	2.46 ± 1.34	1.56 ± 0.70	2.47 ± 0.10	3.14 ± 0.91
21	1.91 ± 1.29	2.44 ± 0.04	4.13 ± 0.40	1.27 ± 0.40	2.32 ± 0.09	3.90 ± 2.40
29	2.19 ± 0.88	2.52 ± 0.08	3.68 ± 1.24	1.88 ± 0.52	2.30 ± 0.08	4.21 ± 1.27
36*	3.06 ± 2.16	2.57 ± 0.10	5.44 ± 0.36	1.86 ± 0.23	2.51 ± 0.11	5.75 ± 1.75
42	2.36 ± 0.96	2.57 ± 0.05	1.50 ± 0.43	2.83 ± 1.04	2.50 ± 0.72	2.19 ± 0.79
49	2.59	2.53 ± 0.09	2.81	3.35 ± 0.96	2.46 ± 0.06	3.28 ± 1.38

* The malnutrition phase of the experiment was terminated at day 36. On day 37, five PCM rats were refed and samples during the refeeding made at day 42 and 49. Six PCM rats died between days 32 and 36.

bile, four replicas per sample. The plate was placed in a humid 37 C incubator for 1 hour, and then washed three times with PBS-Tween 20. Conjugated horseradish peroxidase-IgG (IgG specific for rat S-IgA) (Jackson Immunoresearch Labs, Inc., West Grove, PA) was diluted 1:5000 with PBS-Tween 20, then added to the plate, 200 µl/well. The plate was incubated 1 hour at 37 C and washed three times with PBS-Tween 20. During this interim, a horseradish peroxidase substrate solution was prepared using 0.04% o-phenylenediamine dihydrochloride and 0.04% of 30% H_2O_2 in a 0.1M citric acid 0.2 M Na_2HPO_4 buffer. After the plate was washed, 200 µl/well of substrate solution was added and the rection was allowed to proceed 15 minutes ± 2 seconds at room temperature. The reaction was stopped by the addition of 50 µl/well of 2.5 N H_2SO_4 and the optical density of each well was determined with a Multiskan microtitre plate reader blended with air using the 492 mm filter (Flow Laboratories, Inc., McLean, VA). Sample values were obtained by interpolation from linear regression of the standard curves. Total bile protein was measured by a colorimetric micro-Kjeldahl method (SIGMA bulletin 690).

Results

On day 0, 10 rats were operated on and their bile ducts were cannulated. Bile was collected for 30 minutes. The average flow of bile was 1.42 ± 0.59 ml/hr. The average total protein content of the bile collected was 2.52 ± 0.05 mg/ml, whereas the average concentration of S-IgA was 2.74 ± 0.73 mg/ml (Table 1).

The 2% agar diet used in many previous experiments produced a predictable weight loss with minimal malnutrition-related mortality.[8-10] The female Fisher rats in the control group weighed 124.4 ± 14.5 g at the beginning of the experiment. These rats fed a "normal" diet of rat chow gained weight, 29.1 ± 9.3 g. Rats fed a 2% agar protein depletion diet (USP XV) loss weight (44.4 g) to 83.0 ± 2.6 g during the experiments. The weight changes at the extreme of the experiment (36 days) are statistically significant ($p < 0.001$). Immune function such as survival from *Escherichia coli*-Hb peritonitis usually differs from control after 14 days of the 2% agar protein depletion diet.[7,9,10] The experiment represents an extreme nutritional challenge to the immune system.

On day 7, another two groups of five rats, one control and one PCM, were studied. The bile ducts were cannulated and bile was collected for 30 minutes. The control rats had an average flow rate of 1.54 ± 0.58 ml/hr, an average total protein content of 2.61 ± 0.10 mg/ml, and an S-IgA concentration of 1.68 ± 0.77 mg/ml. In the PCM rats, the average bile flow rate was 1.44 ± 0.49 ml/hr, an average total protein value was 2.4 ± 0.07 mg/ml, and an average S-IgA concentration was 1.95 ± 0.54 mg/ml.

On day 14, another five rats from each group were operated on and bile was collected. The control rats had an average flow rate of 1.62 ± 0.16 ml/hr, an average total protein value of 2.55 ± 0.05 mg/ml, and an S-IgA concentration of 2.46 ± 1.34 mg/ml. The PCM rats had an average flow rate of 1.56 ± 0.70 ml/hr, an average total protein value of 2.47 ± 0.10 mg/ml, and an average S-IgA concentration of 3.14 ± 0.91 mg/ml.

On day 21, another five rats from each group were operated on and bile was collected. The control rats had an average flow rate of 1.91 ± 0.29 ml/hr, an average total protein value of 2.44 ± 0.04 mg/ml, and an S-IgA concentration of 4.13 ± 0.40 mg/ml. The PCM rats had an average flow rate of 1.27 ± 0.40 ml/hr, an average total protein value of 2.32 ± 0.09 mg/ml, and an average S-IgA concentration of 3.90 ± 2.40 mg/ml.

On day 29, another five rats from each group were

TABLE 2. *Data Analysis: Day 36*

	PCM	Control	p value
Wt (g)	−44.4 ± 12	19 ± 10.7	<0.001
Total protein (bile) mg/ml	2.51 ± 11	2.57 ± 10	NS
S-IgA (mg/ml)	+3.01 ± 1.02	1.69 ± 63	NS

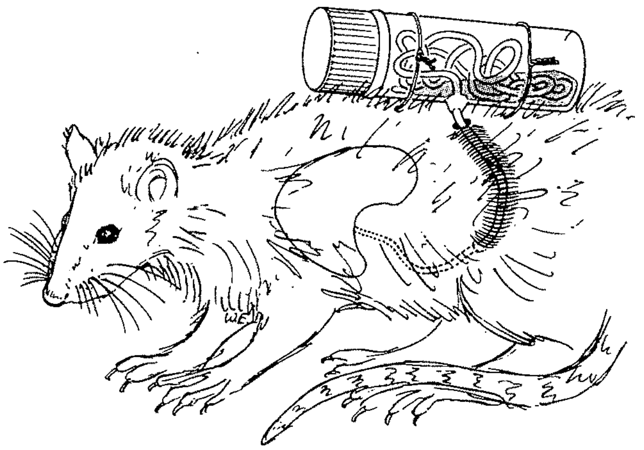

FIG. 1. Rat biliary sampling preparation.

operated on and bile was collected. The control rats had an average flow rate of 2.19 ± 0.88 ml/hr, and average total protein value of 2.52 ± 0.08 mg/ml, and an S-IgA concentration of 3.68 ± 1.24 mg/ml. The PCM rats had an average flow rate of 1.88 ± 0.52 ml/hr, an average total protein value of 2.30 ± 0.08 mg/ml, and an average S-IgA concentration of 4.21 ± 1.27 mg/ml.

On day 36, another five rats from each group were operated on and bile was collected. The control rats had an average flow rate of 3.06 ± 2.16 ml/hr, an average total protein value of 2.57 ± 0.10 mg/ml, and an S-IgA concentration of 5.44 ± 0.36 mg/ml. The PCM rats had an average flow rate of 1.86 ± 0.23 ml/hr, an average total protein value of 2.51 ± 0.11 mg/ml, and an average S-IgA concentration of 5.75 ± 1.75 mg/ml.

On day 37, five PCM rats were refed with standard rat chow and on day 42 bile was again collected. The five control rats had an average flow rate of 2.36 ± 0.96 ml/hr, an average total protein value of 2.57 ± 0.05 mg/ml, and an S-IgA concentration of 1.50 ± 0.43 mg/ml. The PCM rats had an average flow rate of 2.83 ± 1.04 ml/hr, an average total protein value of 2.50 ± 0.72 mg/ml, and an average S-IgA concentration of 2.19 ± 0.79 mg/ml.

On day 49, the experiment was terminated and samples of bile were collected from the rest of the rats. The control rats had an average flow rate of 2.59 ml/hr, an average total protein value of 2.53 ± 0.09 mg/ml, and an S-IgA concentration of 2.81 ± mg/ml. The PCM rats had an average flow rate of 3.25 ± 0.96 ml/hr, an average total protein value of 2.46 ± 0.06 mg/ml, and an average S-IgA concentration of 3.28 ± 1.38 mg/ml.

Statistical analysis, using 95% confidence interval, was established using a pooled t-test and the levels of IgA and total protein for the PCM and control rats were found to be statistically the same ($p < 0.05$). These results suggest that protein–calorie malnutrition minimally affects the levels of biliary IgA and protein, which did not significantly ($p < 0.05$) change during a 36-day period of a protein depletion diet (Table 2).

Discussion

One of the major defense mechanisms against bacterial and viral invasion through mucosal surfaces is from secretory immunoglobulins, *i.e.,* S-IgA and S-IgM, and secondarily, IgE, IgG, and IgD. Immunoglobulin A (IgA) is in secretions of the gastrointestinal and respiratory tracts as well as in milk and saliva.

The origin of IgA in the gastrointestinal tract appears to be from lymphoblastic cells of the gut-associated lymphoid tissue (GALT) which differentiates to precursor IgA producing plasma cells.[11,12] The plasma cells located in the lamina propria of the intestine are stimulated by intestinal antigens that "leak" or are transported by specialized membranous epithelial cells (M-cells) to produce S-IgA (dimeric form). In the presence of IgA deficiency, S-IgM will be increased as compensatory measure.

Secretory IgA differs from serum IgA in that IgA is bonded tightly to the J-chain and is secreted into the crypts of the mucosa. It is also linked to the secretory component (SC), which protects the molecule from proteolytic enzymatic action in the intestine.[13,14]

In the bile, approximately 60% of the IgA is in the S-IgA form. Serum IgA is transported into the hematocytes and is transformed into the polymeric form.[15,16] It is then secreted into the bile. In bile duct obstruction, S-IgA is increased in the serum. On relief of the obstruction, the level of S-IgA in the serum returns to normal levels.

The action of S-IgA is protective and binds with intestinal antigens. It neutralizes bacterial and viral enterotoxins along with agglutinization of the organisms. It also functions to prevent the attachment of bacteria to the surface epithelium. This function is important in infections such as Streptococcal pharyngitis or cholera. S-IgA does not seem to have any clearcut effect on the complement system, although bacteriolytic action *via* the complement system has been described.[17] Human serum antibody responses are variable and are probably due to the nature of the antigen, the amount involved, the age of the patient, and the route of infection.

Protein–calorie malnutrition (PCM) is associated with many immunologic defects. PCM causes an increased gastrointestinal permeability to antigenic factors. In severely malnourished children, a selective decrease in secretory IgA levels in intestinal secretions occurs. PCM is associated with an increased incidence of intestinal infection, circulating antibodies to food and bacterial antigens, and evidence of autoimmune disease. Paradoxically, some studies of children who have kwashiorkor reveal T-cell lymphokin levels—migration inhibition factor (MIF) and leukocyte migration inhibition factor (LMI), which are similar to normal children.[18] However, studies by Sirisinha et al. found S-IgA levels decreased in children who have PCM.[19]

Our study was undertaken to determine if the S-IgA levels of bile in rats were lowered by malnutrition. The weight of the Fisher rats in PCM and control rats was predictable. The weight of PCM rats decreased from an average weight of 127.4 ± 14.5 g at day 0 to 83 ± 2.6 g on day 37, whereas the control rats' weight increased from 124.4 ± 14.5 g on day 0 to 153.6 ± 3.8 g on day 37. The control rats, who were fed a normal diet, increased in weight and appeared healthy. The levels of S-IgA in PCM rats increased from 2.74 ± 0.73 mg/ml on day 0 to 5.75 ± 1.75 mg/ml on day 37, as did the control rats' S-IgA levels increase from 2.74 ± 0.73 mg/ml to 5.44 ± 0.36 mg/ml. Both the PCM and control rats' S-IgA levels similarly increased despite the PCM rats losing weight and the control rats gaining weight. These results suggest that the immune system of the gut may be of great importance and appears to be maintained, whereas other bodily systems deteriorate in the presence of malnutrition.

The total biliary protein level on day 0 was 2.52 ± 0.05 mg/ml and on day 36 was 2.51 ± 0.11 mg/ml for PCM rats and 2.57 ± 0.10 for the control rats. The total biliary protein levels remained constant in both the PCM and control rats. Even in the absence of sufficient protein, PCM rats maintained a constant biliary protein level. No differences occurred between the control rats and the PCM rats in terms of total protein and S-IgA concentrations in their bile.

Prior experiments of *E. coli*-Hb adjuvant peritonitis and other immune studies show that rats of this breed, age, and sex become highly susceptible to infection at 14 days. During 14–21 days of a 2% agar diet, weight loss is approximately 25% of starting weight. One to two weeks of the diet causes substantial loss of body protein and fat. The model results in pronounced loss of weight and protein in the small intestine as well.

It is surprising that IgA, the "antiseptic paint" of the gastrointestinal tract is maintained in severe malnutrition. It is especially surprising that IgA is well preserved in PCM because of the well-known atrophy of the small intestinal mucosa associated with malnutrition. Because the intestinal mucosa comes into greatest contact with foreign antigens, bacteria, and viruses, constant levels of S-IgA aid in maintenance of protection against ingested bacteria, viruses, and other antigens. It appears the biliary S-IgA is a protein of high biologic priority.

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DISCUSSION

DR. GEORGE L. JORDAN, JR. (Houston, Texas): We are indebted to Drs. Sheldon and Lim for the information contained in this paper. Immunology has been a subject of interest to surgeons over a good many years now, but actually only a few surgeons are conducting serious experimental studies. The subject of secretory immunoglobulins is almost nonexistent in the surgical literature. In fact, I had a computer search of the recent literature and found only one other recent article, and that was by Dr. Sheldon and his group. That particular article showed that secretory IgA in the bile decreased in animals fed intravenously and that oral food intake was necessary in maintaining normal levels. This study shows that restricting protein in the diet did not reduce IgA secretion in the bile of animals in this experiment. These studies are obviously of great importance to the general surgeons, because the bacteria which enter through the gastrointestinal tract are the cause of intra-abdominal infections following gastrointestinal surgery in most cases. I don't pretend to be an expert in this area myself, but this study raises several questions.

1. Dr. Sheldon, do you believe that the decrease in IgA secretion of the bile in animals on intravenous feeding simply represents the lack of stimulation resulting from food, or is it a contributing factor to sepsis in the critically ill patient in our ICU's?
2. Studies by others have demonstrated that vitamin A deficiency does reduce secretory IgA in the bile. Did these animals have a normal vitamin intake during the time of their protein deprivation, and have you evaluated other dietary-restricted programs?
3. Other investigators believe that the rat is not the optimum experimental animal, and state that the spectrum of immunoglobulins in the bile of the rat is not just like that in the human, and that there are other animals, such as the dog, in which there is a greater similarity between the two. Have you done studies in other animals, and particularly, have you done studies on human bile—for example, in patients that have a T-tube in place for a prolonged period?
4. Do you believe that there are methods which might increase the concentration of secretory IgA?
5. Do you believe that the determination of IgA in human bile or other gastrointestinal secretions might allow selection of patients who need special protection from infection in the postoperative period?
6. Have you studied any other immunoglobulins in the bile or in other fluids in the gastrointestinal tract? It is my understanding that immunoglobulins other than IgA are present in human bile in significant concentrations as compared to IgA, in contradistinction to the rat.

DR. CAROL E. H. SCOTT-CONNER (Jackson, Mississippi): The importance of the gut as a component of host defense has long been recognized. The gut-associated lymphoid tissue is exposed to and processes a vast array of foreign antigens. Immunoglobulin A forms a crucial part of this defense against the translocation of intraluminal bacteria.

The experimental data presented by Dr. Sheldon nicely demonstrates that secretion of biliary IgA is not impaired in malnourished rats and underscores the teleological importance of this substance.

I would like to ask Dr. Sheldon to consider the role of IgA in the host defense impairment noted in extrahepatic biliary obstruction.

In mechanical biliary obstruction, biliary secretion of IgA is blocked, and intraluminal IgA levels may fall. This decrease in biliary secretory IgA might contribute to the profound suppression in reticuloendothelial and lymphocyte function noted in extrahepatic biliary obstruction.

There are experimental data to suggest that internal biliary drainage which restores the intrahepatic circulation mitigates many of the adverse effects noted in obstructive jaundice.

In contrast, external biliary drainage, while effective in decreasing the level of jaundice, does not. Restoration of intraluminal bile salts has been implicated as one possible mechanism. Increase in intraluminal biliary secretory IgA levels might be another.

I would like to ask whether you have looked at biliary secretory IgA levels in rats with mechanical biliary obstruction using your nice experimental preparation, and, in particular, if you have studied the effect of reversal of obstruction by internal biliary drainage as opposed to external biliary drainage.

DR. R. SCOTT JONES (Charlottesville, Virginia): This was an excellent experiment and an excellent presentation. I think the study was designed and analyzed critically.

Dr. Sheldon has introduced a concept of studying immunoproteins in bile that I think will stimulate further study.

I had an opportunity to read his manuscript and wanted to make one particular comment about his method of data analysis and the conclusion of his study. The principal information regarding the bile secretion in these rats that was presented included bile flow presented in mls per hour and IgA concentration in mgs per ml. And using those two parameters, he concluded that the secretion was similar in the experimental and control groups.

Another parameter of interest would be the total IgA secretion in these animals per unit time. In other words, if you multiply the volume of bile times the concentration of the immunoglobulin, you would then understand the total amount of IgA secreted per unit time, which may be a very important observation.

A very brief and rough calculation from the data would suggest to me that at the end of the period of starvation, if one did such a calculation, then the total output of IgA in the control animals would exceed the experimental approximately threefold. Whether that had statistical significance would certainly bear examination.

This is probably a very important mechanism, not only in biliary infections, but also the maintenance of the flora and minimizing of invasive infections in the G-I tract. I think this is truly creative work and extremely well done, and I want to compliment Dr. Sheldon and his colleagues on this important contribution.

DR. GEORGE F. SHELDON (Chapel Hill, North Carolina): I would like to thank the discussants for their kind comments. I especially appreciate Dr. Jones's, because I do think that this is new enough that we may not be looking at the parameters as we should. I am very grateful for that suggestion.

Dr. Scott-Conner, I appreciate your comments; we have not done any experiments with mechanical obstruction. Your suggestions and comments need to be examined. The obstructed bile duct is easy to produce. It may well be that IgA will be inactivated by obstruction, which may be what you are suggesting.

Dr. Jordan has raised all the questions. For most of them, I lack answers.

The decrease of IgA with I.V. feeding has shown that intraluminal presence of foodstuffs is necessary for IgA production.

(Slide) As to the type of diet, it is a standard diet made by USP and is called "2% Agar Protein Depletion Diet." It has a lot of vitamin A.

As animals and people become malnourished, the kinetics of interaction among vitamins and trace elements become complicated. What are sufficient quantities of vitamins and trace metals at one point in time may be insufficient later.

Are there methods to increase IgA? You probably could with some antigenic stimuli that could be ingested.

The question about other immunoglobulins is a good one. In this model, as shown by a French investigator, 90% of the immunoglobulin in this type of animal is IgA, so it is valid for this experiment. Whether it is valid in all instances in unknown. Patients with congenital absence of IgA and other dysgammaglobulinemias do not have a high incidence of intestinal infections. They have low IgA, but the other immunoglobulins are elevated.

Again, I would like to thank everyone for their comments. I would like to thank the Association for the privilege of membership and Dr. David Saviston, Dr. Richard Meyer, and Dr. Colin Thomas for their sponsorship for membership.

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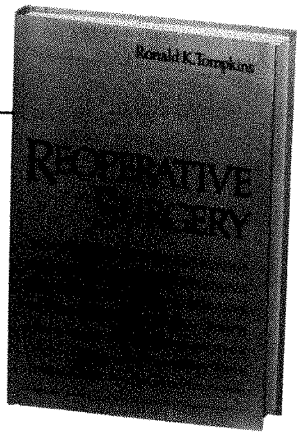

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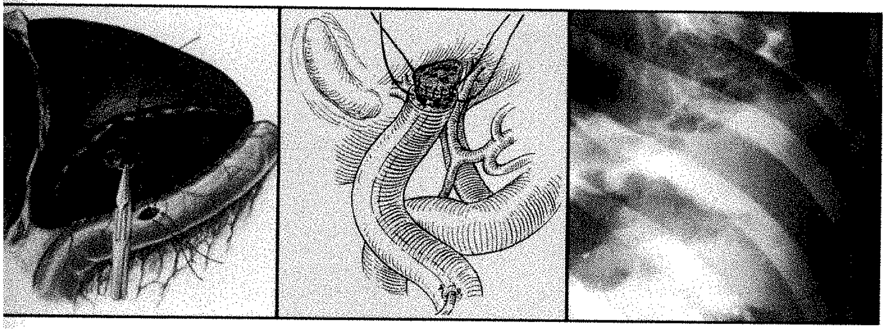

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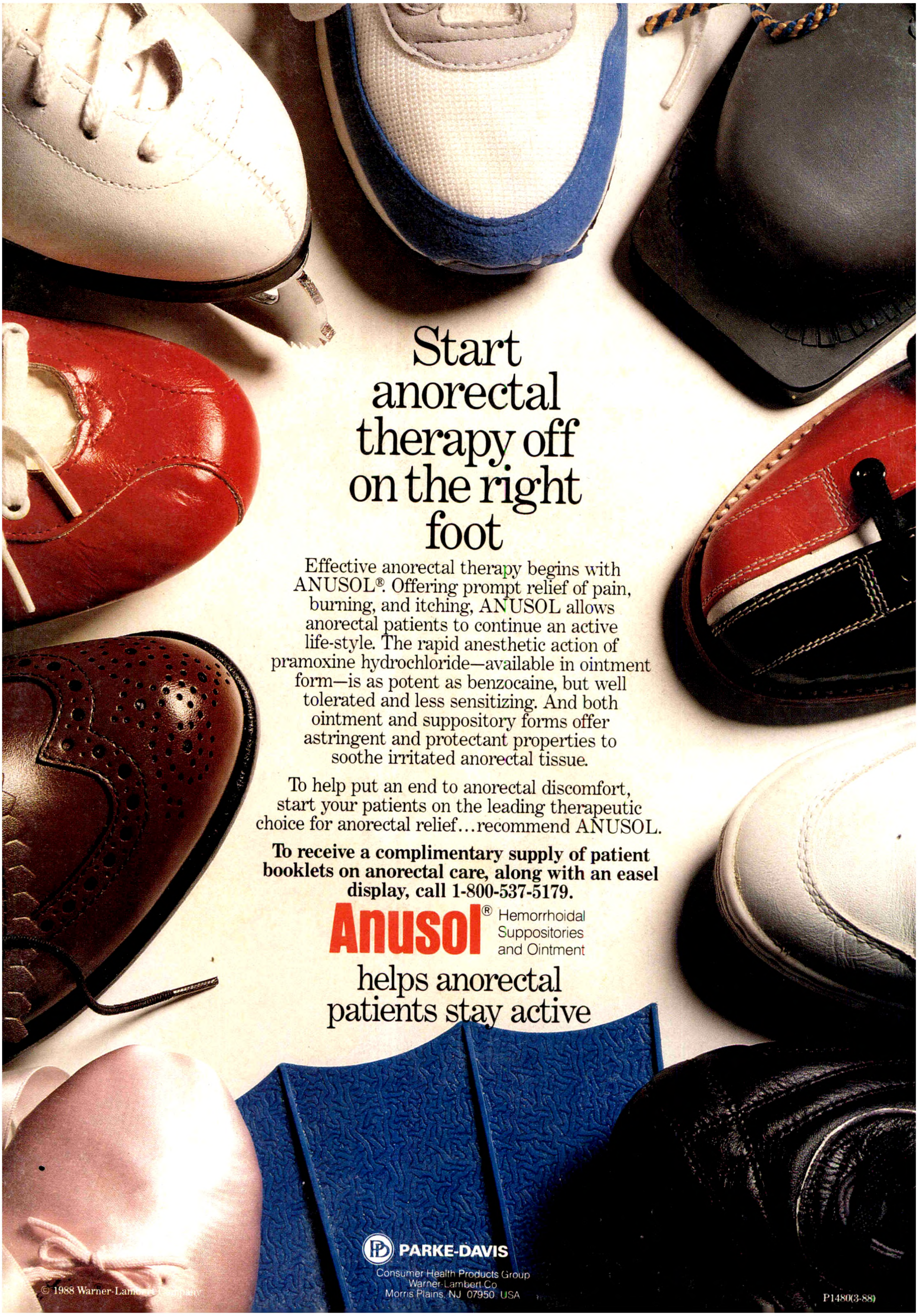

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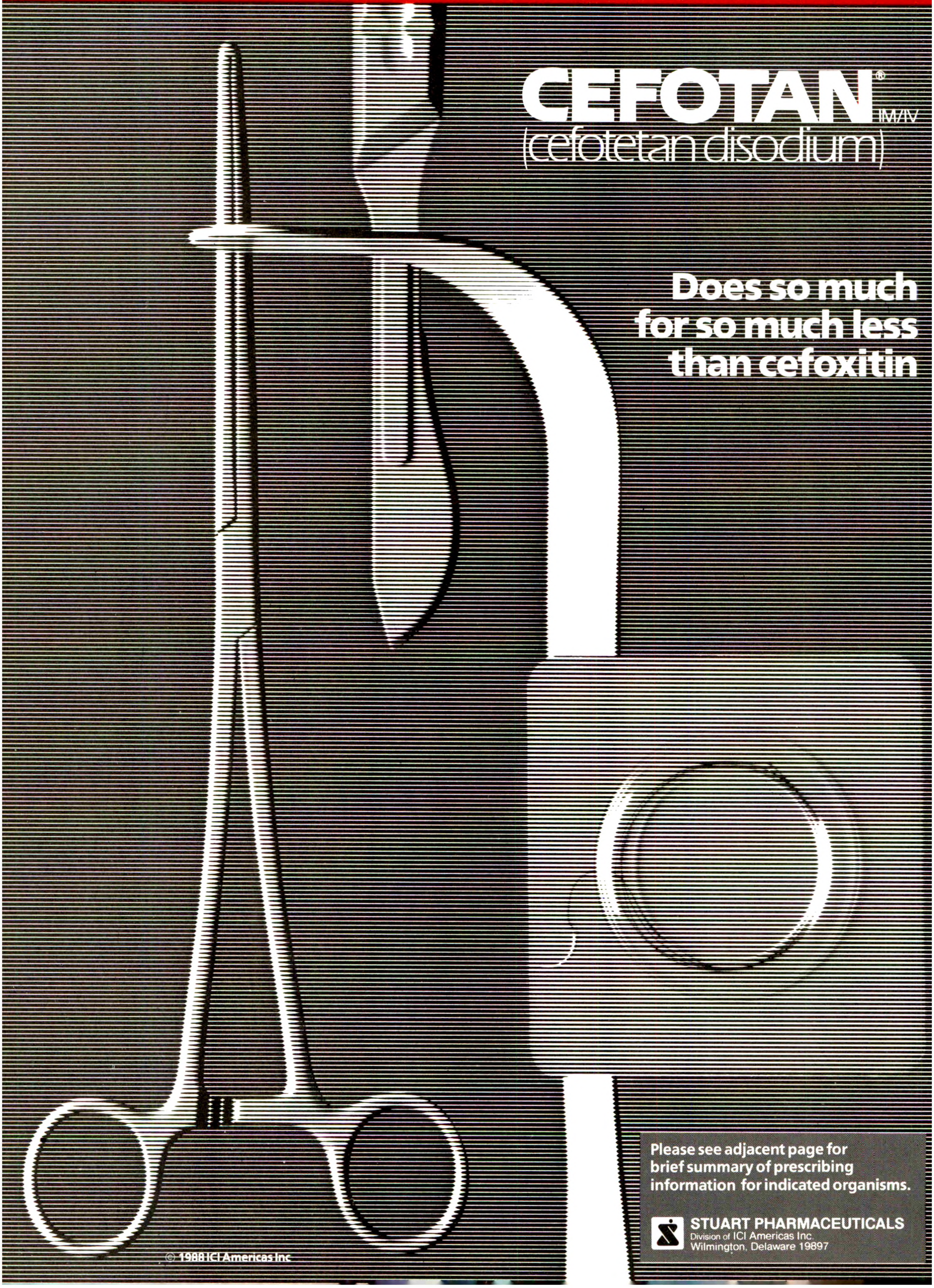

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TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary tract infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris*, *Providencia rettgeri*, and *Morganella morganii*).

Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.

Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.

Gynecologic infections caused by *Staphylococcus aureus*† (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*,* *Streptococcus* species (excluding enterococci), *E coli*, *Proteus mirabilis*, *Neisseria gonorrhoeae*, *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*), *Fusobacterium* species,† and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species†).

Intra-abdominal infections caused by *E coli*, *Klebsiella* species (including *K pneumoniae*†), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*).

Bone and joint infections caused by *Staphylococcus aureus*.†

***NOTE:** Some strains of *Staphylococcus epidermidis* are resistant to cefotetan.

† Efficacy for this organism in this organ system was studied in fewer than ten infections.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.

PRECAUTIONS

GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state. Prothrombin times should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels of Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approx 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approx 2-4 times the usual human dose), only 1 of 10 treated animals was affected, and the degree of degeneration was mild. Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In clinical studies the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5 percent of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4 percent of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2 percent of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2 percent of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than one percent of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500).

DOSAGE AND ADMINISTRATION

TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dose*	Every 12 hours
10-30	Usual Recommended Dose*	Every 24 hours
<10	Usual Recommended Dose*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED

CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

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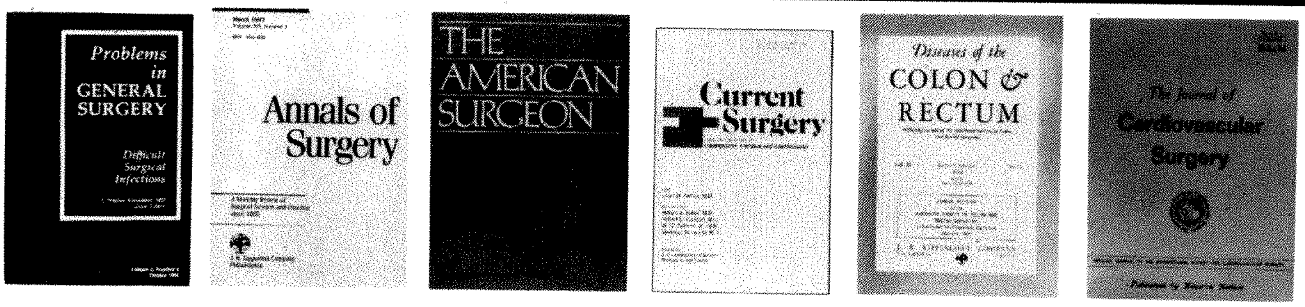
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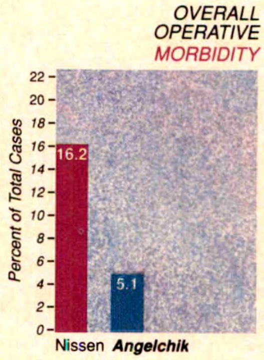
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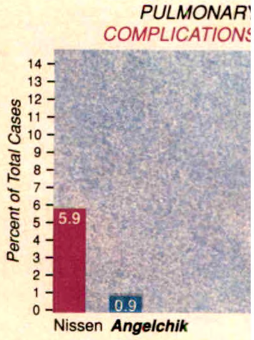
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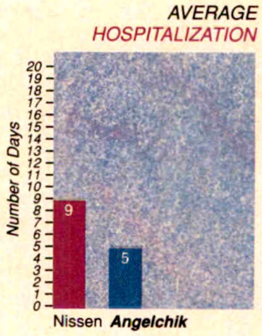
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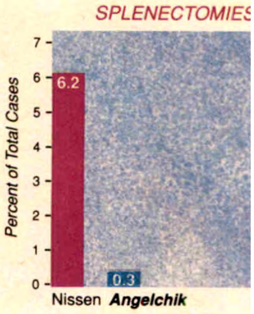
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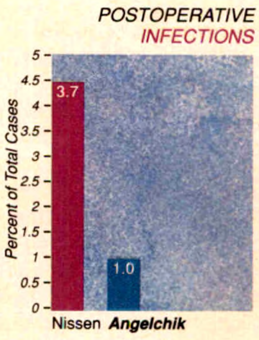
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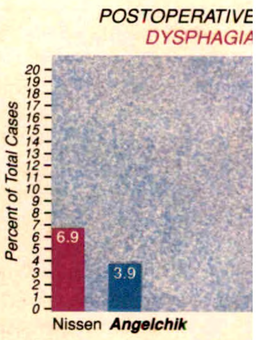
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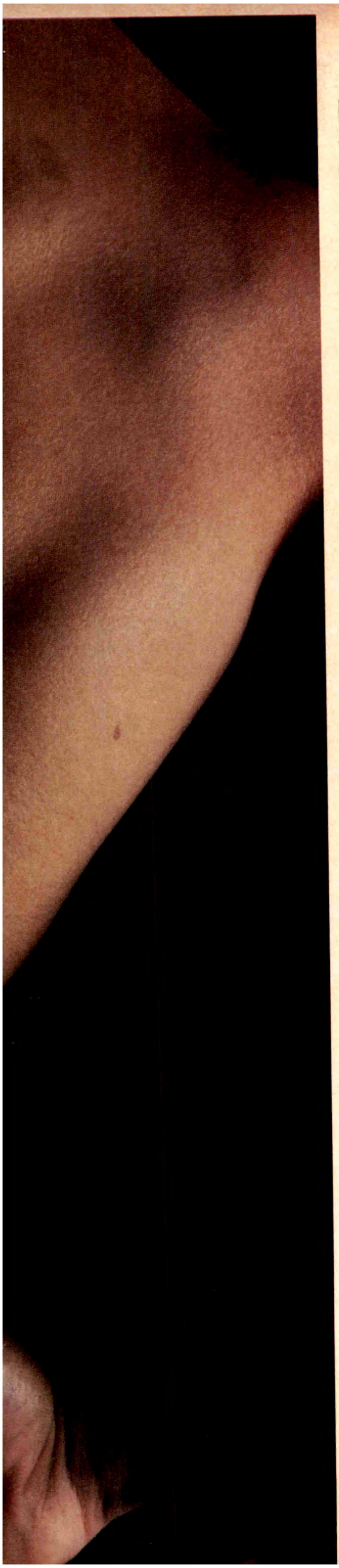

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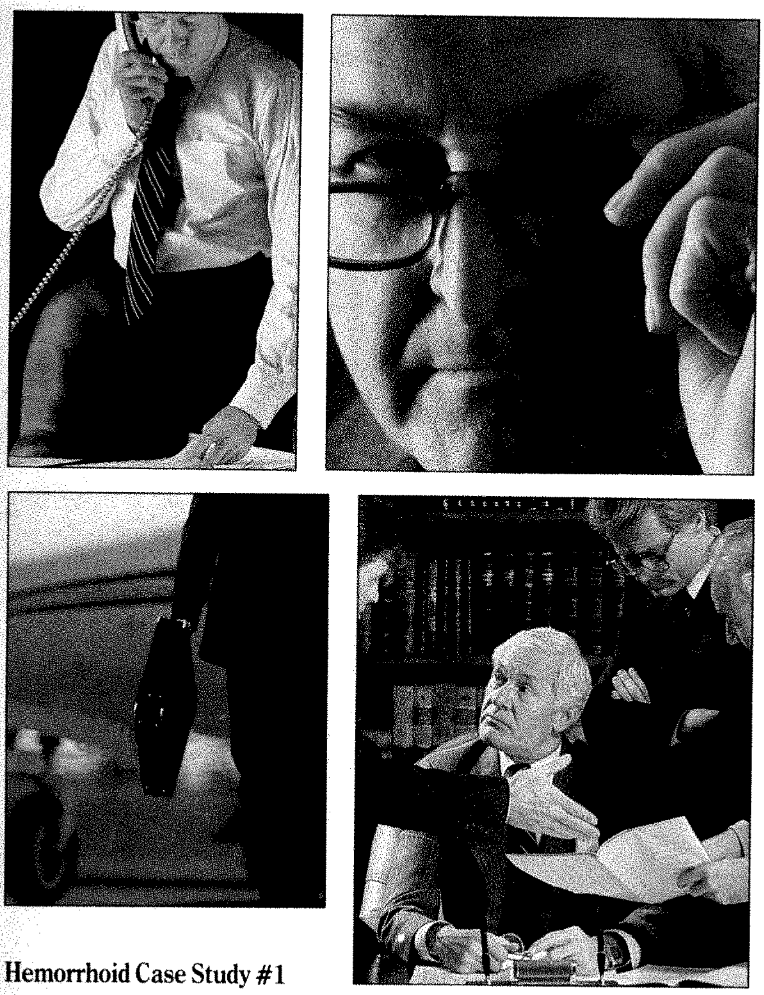

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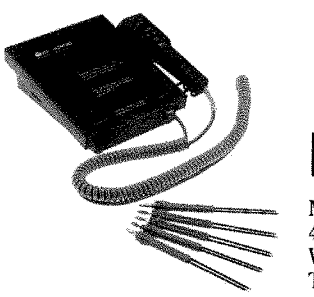

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[1] National Center for Health Statistics for 1985.

[2] A complete list of clinical evaluators is available upon request.

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Alcohol Protects Against Cholesterol Gallstone Formation

WAYNE H. SCHWESINGER, M.D.,* WILLIAM E. KURTIN, PH.D.,† and ROBBIE JOHNSON*

Epidemiologic studies have suggested that alcohol intake may protect against cholelithiasis. Gallstone formation was studied in 20 prairie dogs fed a 0.4% cholesterol-supplemented liquid diet. In ten animals, ethanol provided 35% of total calories. In ten pair-fed controls, ethanol was replaced with isocaloric maltose. After 3 months the gallbladders were inspected for gallstones, and gallbladder bile was analyzed. Cholesterol macroaggregates were present in all controls and pigment concretions were noted in five. No stones were observed in ethanol-fed animals. Bile in the ethanol group contained less cholesterol than the controls (5.60 ± 0.71 *vs.* 9.16 ± 0.61 mmol/L, $p < 0.05$) while phospholipids, total bile acids, and bilirubin were unchanged. The resulting cholesterol saturation index was reduced in the ethanol group (0.81 *vs.* 1.22, $p < 0.05$). The ratios of trihydroxy to dihydroxy bile acids were also different (2.07 ± 0.25 in ETOH *vs.* 3.29 in controls, $p < 0.05$). The bile calcium concentration was higher in control animals presumably secondary to the use of complex sugars (5.36 ± 0.37 *vs.* 3.77 ± 0.32 mmol/L, $p < 0.05$). These results confirm that ethanol inhibits cholesterol gallstone formation. They further suggest that this effect is dependent on reductions of biliary cholesterol and selective changes in bile acid concentrations.

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THE INFLUENCE of ethanol on cholelithiasis is still incompletely understood. In autopsy studies the prevalence of gallstones appears to be increased when alcoholic cirrhosis is present.[1,2] This finding is explained largely by an increment in pigment stone formation.[3,4] Cholesterol stones, in contrast, are reported only infrequently in cirrhotic patients who undergo cholecystectomy.[5,6] Moreover, epidemiologic surveys have suggested the intriguing possibility that biliary disease may actually be decreased by alcohol ingestion. In the Framingham study, the amount of alcohol consumed appeared to have an inverse relationship to the incidence of definite gallbladder disease, although this effect did not reach statistical significance.[7] Similarly, data from the Kaiser-Permanente cohort indicated that heavy drinkers had a risk of hospitalization for cholelithiasis, which was only one-third that for nondrinkers.[8] More recently, Scraggs et al. have reported a case control study of 267 patients with gallstones carefully matched to both community and hospital controls. They also noted that the consumption of alcohol was associated

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with a substantial decrease in the prevalence of gallstones.[9]

Because the prairie dog has been shown to be a useful model for the study of various aspects of lithogenesis, the effects of oral ethanol in this animal were investigated. Ethanol administered as 35% of total calories prevented cholesterol stone formation. This protective effect was accompanied by changes in both bile acid distribution and biliary calcium concentration as well as by a relative cholesterol desaturation.

Materials and Methods

Animals and Diet

Twenty adult male prairie dogs (cynomys ludovicianus) weighing 0.6–1.4 kg were obtained from Otto M. Locke (New Braunfels, TX) and individually housed in a thermoregulated room (23–25 C). During a 2-week adaptation period the animals were fed a standard laboratory chow containing negligible cholesterol (Teklad, Madison, WI). They were then divided into pairs with the members matched in weight as closely as possible. Animals were pair-fed a commercially prepared, nutritionally complete semisynthetic liquid diet as the sole source of oral intake (Bioserv, Inc., Frenchtown, NJ). Experimental animals received a diet containing 0.4% cholesterol by weight to which ethanol was added to provide 35% of total calories. Previous experiments have demonstrated that this diet results in peak serum ethanol levels of 240–320 mg/dL. Control animals received an identical cholesterol-supplemented diet except that ethanol was replaced by equicaloric amounts of maltose–dextrin. Both diets were kept refrigerated in darkness in their dry form to minimize cholesterol oxidation and were reconstituted on alternate days.

At the end of 90 days, the prairie dogs were anesthetized and a celiotomy was performed. The common bile duct was cannulated with polyethylene tubing, the cystic duct ligated, and the gallbladder aspirated. One drop of gallbladder bile was examined under light and polarizing microscopy for biliary crystals.[10] The remaining gallbladder bile was frozen and stored for subsequent analysis. Measurements of hepatic bile flow were conducted for 1 hour. Blood was collected by cardiac puncture, allowed to clot and then centrifuged, after which serum was carefully aspirated and frozen. The gallbladders were removed, opened longitudinally, and inspected for stones. The animals were then killed with an intracardiac injection of T-61 Euthanasia Solution (Hoechst, Somerville, NJ).

Biochemical Analyses

Prior to analysis, frozen bile was rewarmed in a 37 C water bath and centrifuged for 5 minutes at 2000 rpm. Cholesterol content was determined using a commercial colorimetric assay kit based on the enzymatic oxidation of cholesterol (Sigma Diagnostics, St. Louis, MO). Total phospholipids were also measured enzymatically using the color reagent described by Qureshi et al.[11] and the method of Takayama et al.[12] Bile acids were determined by high performance liquid chromatography (HPLC) as described previously.[13] The column was a Microsorb C18 column (0.5 × 25 cm, Rainin Instrument Co., Inc., Woburn, MA), and the mobile phase was acetonitrile–methanol – 0.03 mol/L phosphate buffer, pH 3.4 (10:60:30). The flow rate was 1 mL/min and detection was at 204 nm using a LDC Spectromonitor D variable wavelength absorbance detector. Conjugated and unconjugated bilirubin were also determined by the method described previously.[13] HPLC was performed on a 25 cm Microsorb C18 column using 0.1 mol/L dioctylamine acetate in methanol as the eluting solvent. The flow rate was 0.75 mL/min and detection was by absorbance at 435 nm. All bilirubin analyses were conducted in dim red light. Total calcium concentrations were determined by atomic absorption spectrophotometry (Varian Instrument Co., Palo Alto, CA).

Quantitative Treatment of Data

All data are reported as mean ± SEM. Statistical comparisons of mean values among groups were assessed by the unpaired Student's t-test. Proportions were evaluated by the chi square test. Cholesterol saturation indices (CSI) were calculated from bile lipid data using the computer program of Kuroki et al.[14] as derived from the critical tables of Carey.[15]

Results

All animals appeared to tolerate the liquid diet without difficulty. Changes in total body weight recorded at the end of the experiment were small, and there was no significant difference in the weight changes (−0.10 ± 0.04 kg for control animals *vs.* −0.13 ± 0.06 kg for ethanol-fed animals).

Gallstone Formation

Upon gross inspection, the gallbladders of all control animals were found to be packed with aggregated cholesterol crystals or cholesterol stones. In addition, several small black concretions were visible in five of the ten control animals. Infrared spectroscopic analysis of one of these black deposits showed that it was composed of approximately 40% calcium bilirubinate by weight. By contrast, no cholesterol macroaggregates or pigment deposits or crystals were found in any of the ethanol animals by either gross or microscopic observation ($p < 0.001$).

TABLE 1. *Gallbladder Bile Composition*

	Control	Ethanol
Cholesterol (mmol/L)	9.2 ± 0.7	5.6 ± 0.7*
Bile salts (mmol/L)	146.9 ± 10.0	152.2 ± 11.1
Phospholipids (mmol/L)	20.0 ± 1.5	16.7 ± 1.3
Total lipids (mmol/L)	176.1 ± 11.7	174.4 ± 12.5
CSI	1.16 ± 0.02	0.80 ± 0.06*
Cholesterol:phospholipid ratio	0.46 ± 0.01	0.34 ± 0.03*
Total calcium (mmol/L)	5.49 ± 0.38	3.77 ± 0.35*
Unconjugated bilirubin (μmol/L)	10.8 ± 1.4	11.2 ± 2.6
Conjugated bilirubin (μmol/L)	183.5 ± 27.3	162.2 ± 29.0

* $p < 0.05$.

Hepatic Bile

Bile flow rate was measured at the time of hepatic bile collection. The difference found between the flow rates of the two groups approached but did not reach significance (0.7 ± 0.2 mL/h for control animals *vs.* 1.2 ± 0.2 mL/h for alcohol animals).

Gallbladder Bile

Analytic data for the major components of gallbladder bile in both control and ethanol groups are presented in Table 1. The mean cholesterol level was lower in the ethanol-fed animals by a factor of almost 2. Total bile salt concentrations were the same in the two groups, while phospholipid values were slightly, but not significantly, lower in the alcohol group. Total lipid concentrations were equal. The difference in cholesterol levels resulted in a significant difference in the CSI for the biles of ethanol and control animals. In the case of controls, the CSI of all biles was greater than 1, while in the ethanol group only one bile had a CSI greater than 1 (Fig. 1). In addition, the cholesterol:phospholipid ratio was significantly lower in the alcohol group. Although no difference was found in the concentration of total bile salts in the two experimental groups, marked changes did occur in the levels of specific bile salts. The changes in the major bile salts are summarized in Table 2. A significant increase in the total amount of dihydroxy bile salts was found in ethanol-fed animals. This increase was due in large part to a doubling in the mean concentration of taurochenodeoxycholic acid. At the same time a small decrease in the total amount of trihydroxy bile salts was found in the alcohol group compared to controls. These changes resulted in a decrease of the trihydroxy:dihydroxy bile salt ratio from a value of greater than 3:1 in controls to approximately 2:1 in the ethanol group ($p < 0.005$).

Total calcium concentrations in gallbladder bile were significantly lower in ethanol-fed animals when compared to controls. Unconjugated bilirubin values were the same in both groups. The biles of ethanol animals were found to have a small, but not significant, decrease in the concentration of conjugated bilirubin. The monoconjugated form of the pigment accounted for more than 95% of total bile pigments.

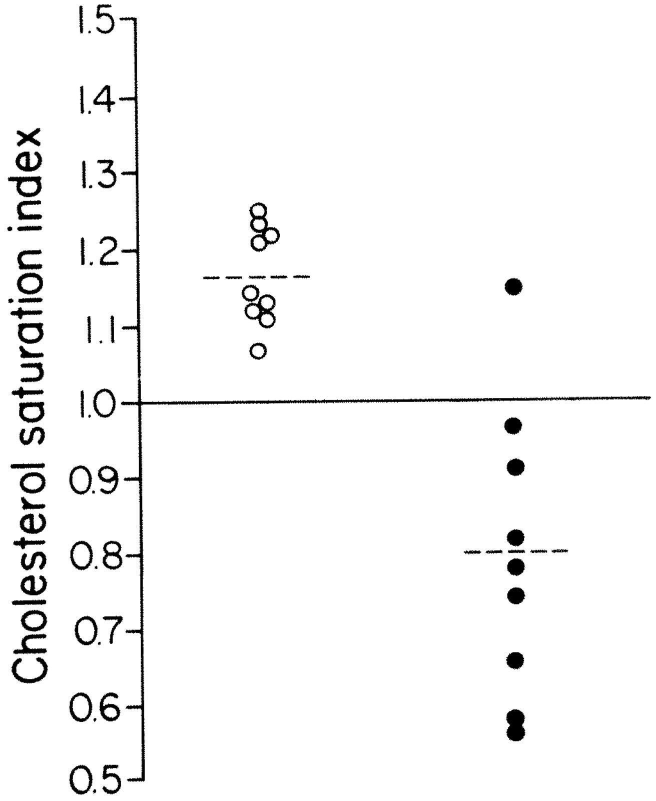

FIG. 1. CSIs are plotted for individual animals. Mean values (----) for control (○) and ethanol-fed (●) groups are significantly different ($p < 0.05$).

Discussion

Although epidemiologic studies have indicated that moderate alcohol intake reduces the risk of biliary disease, investigations of the mechanisms responsible for this effect have been hampered by serious methodologic problems. To overcome these difficulties, the prairie dog was chosen as the best model for study. In this animal the biliary lipid composition is similar to that of humans and becomes supersaturated with cholesterol when a lithogenic diet is provided.[16] As in humans, cholesterol

TABLE 2. *Bile Salts in Gallbladder Bile*

	Control	Ethanol
Taurocholic acid (mmol/L)	110.0 ± 7.5	97.5 ± 8.1
Taurochenodeoxycholic acid (mmol/L)	16.6 ± 1.4	35.6 ± 5.4*
Taurodeoxycholic acid (mmol/L)	18.8 ± 2.6	16.5 ± 3.3
Trihydroxy:dihydroxy ratio	3.19 ± 0.16	2.07 ± 0.3*

* $p < 0.005$.

lithogenesis then proceeds from the supersaturation phase through both crystal nucleation and stone growth phases. In these experiments, a liquid diet was used to overcome the natural aversion of prairie dogs to alcohol and to allow accurate pair feeding.[17] This approach ensured that each group received equal calories and nutrients; thus, the effect of nutritional intake alone should be minimized.

At the end of the 3-month study period, it was clear that ethanol administration had effectively prevented cholesterol precipitation and stone formation. In fact, bile samples from the gallbladders of ethanol-fed animals demonstrated no microscopic evidence of cholesterol crystals, indicating a high degree of solubilization. These results parallel those seen when other substances are used to arrest stone formation in the prairie dog such as hyodeoxycholic acid,[18] aspirin,[19] and the bile acid analog, ursodeoxyoxazaline.[20] The diversity of these litholytic substances and their putative mechanisms of action underscores the newly appreciated complexity of cholesterol gallstone formation.

In the current study, multiple factors appeared to be affected by alcohol administration. Notably, the CSI, a numerical approximation of the cholesterol-holding capacity of bile, was significantly lower in the ethanol group. All but one of the biles tested from this group were below unity, the defined point of cholesterol saturation. Conversely, all control biles were supersaturated with cholesterol. On this basis alone one would expect that no cholesterol monohydrate crystals would precipitate in ethanol-treated animals because cholesterol saturation is a necessary although not sufficient prerequisite for stone formation.[21] These results are similar to those of Thornton et al.[22] who found a decreased CSI in the bile of healthy human volunteers maintained for 6 weeks on moderate alcohol intake.

The reduction of the CSI in this model was largely accounted for by a significant decrease in the concentration of cholesterol in gallbladder bile. Decreases in biliary cholesterol output have previously been observed in association with ethanol administration in biliary fistula dogs[23] and in patients with cirrhosis.[24] Such a decrease in bile cholesterol promotes its complete solubilization by incorporation into either mixed micelles or phospholipid vesicles. This effect of long-term ethanol administration could be caused by a variety of mechanisms including a decrease in the intestinal uptake of cholesterol or modification of the hepatic regulatory pathways. Little information is available concerning cholesterol absorption during periods of alcohol ingestion. However, because it is predominantly a passive process, it is not likely to be greatly changed.[25] In one of the few reported studies, a slight enhancement of cholesterol uptake was noted to occur following the acute administration of ethanol to rabbits.[26]

Conflicting data have been published concerning the effect of ethanol on hepatic rate-limiting enzymes. The activity of HMG-CoA reductase, the enzyme responsible for hepatic cholesterogenesis, has been found to be both increased or decreased in rats fed ethanol for 3 weeks or more.[27,28] This study provides no specific information on this point. Interestingly, there is general agreement among these same authors that ethanol induces a reduction in the activity of the other major rate-limiting enzyme, cholesterol 7-alpha-hydroxylase, which is responsible for the degradation of cholesterol to bile acids. It is not known how this change affects the biliary dynamics of the prairie dog model, although it is cited as a contributory cause for cholesterol accumulation in the liver during ethanol feeding.[29]

Bile salts are essential to cholesterol solubilization because of their ability to form mixed micelles. In this study, the total bile salt concentrations in the gallbladder were not statistically different between groups. Other investigators have noted that chronic ethanol feeding results in increased bile acid output in animals.[30,31] However, Nestel et al.[32] found no change in normal humans who consumed ethanol as 37% of calories. Moreover, once cirrhosis develops, the size of the total bile acid pool is decreased mostly as a result of selective reductions in deoxycholic acid and cholic acid.[24]

Importantly, the size of the bile acid pool is also not the only critical factor in the solubilization of cholesterol, but the specific distribution of bile acids must also be considered. Thus, Carulli et al.[33] have observed that the hydrophilic–hydrophobic balance of bile salts helps to determine the capacity of bile to maintain cholesterol in solution. The trihydroxy bile acids, because they are more hydrophilic than the dihydroxy bile acids, are less effective solubilizers of cholesterol. In this regard, the ratio of trihydroxy to dihydroxy bile acids was significantly decreased by ethanol intake. The level of chenodeoxycholate, one of the major dihydroxy bile acids was significantly elevated in animals receiving ethanol. This selective increment is important because of the specific desaturating potential of this agent.[34] The reason for the enhancement of chenodeoxycholate in association with alcohol intake is not known. It is possible that either increased synthesis occurs through an alternate enzymatic pathway[35] or that bacterial dehydroxylation in the intestine is suppressed.[36] Thus, this accumulated data and the work of others suggest that qualitative changes in the bile acid composition of ethanol-treated animals may contribute substantially to the prevention of cholesterol gallstones.

Physicochemical factors other than supersaturation are also important in the modulation of cholesterol solubility, and these may be affected by ethanol. Recently, increasing attention has been focused on crystal nucleation and the role played by the bile salt-independent vesicular mode of cholesterol solubilization. In model systems of supersaturated bile the key determinants of the nucleation time have been found to include the total lipid concentration, the cholesterol:phospholipid ratio, and the Ca^{+2} concentration.[37] In this study, the concentration of total lipids was unchanged, but the cholesterol:phospholipid ratio was significantly lower in the ethanol group, a finding consistent with a prolonged nucleation time. This decrease indicates that fewer cholesterol molecules are incorporated into each phospholipid vesicle resulting in a more stable carrier state.[38]

The finding of an elevated biliary calcium in the control animals and pigment deposits in 50% of the same group was not unexpected; others have noted similar findings in cholesterol-fed prairie dogs and guinea pigs.[16,39] Based on a recent study by Conter et al.[40] it seems likely that the calcium bilirubinate concentrations in the control animals are related to the use of a complex sugar as the equicaloric substitute for ethanol. Conter et al.[40] noted increased concentrations of phospholipid, calcium, and bilirubin in the gallbladder bile of animals on a high carbohydrate diet. In this study, the concentration of calcium was elevated in the control animals when compared to ethanol-fed animals. In addition, values from previous experiments using prairie dogs maintained on nonmodified diets were the same as in the alcohol groups (unpublished observations). The calcium elevation seen in the controls may have been sufficient, however, to result in a calcium–bilirubin solubility product that exceeded the point of saturation. It is also possible that the elevated bile calcium in control animals actually promoted the more rapid nucleation of cholesterol crystals. Calcium is reported to significantly increase the metastability of unilamellar phospholipid–cholesterol vesicles[37] and acts as a pronucleating agent by accelerating cholesterol aggregation and precipitation in model bile solutions.[41]

Overall, these studies document that a major mechanism by which alcohol can protect against cholesterol gallstone formation is to induce changes in the concentration and solubilization of cholesterol itself. Still unresolved is the issue of whether alcohol administration causes significant additional perturbations of other important factors such as nucleation time, gallbladder motility, mucin production, or bile protein secretion.

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DISCUSSION

DR. HENRY PITT (Baltimore, Maryland): First, let me state that I concur with the author's conclusions and believe that this paper is an important contribution that adds to other data which Dr. Schwesinger has reported on the influence of alcohol on bile composition. I have one concern, however, about the control group that was used in this experiment. You compared a high cholesterol/high alcohol diet to a high cholesterol/high carbohydrate diet. This control group may have been appropriate, but were the groups comparable in terms of the relative proportions of carbohydrates, fats, and proteins?

To fully interpret your data, I would have liked to have seen other control groups. For example, a low cholesterol group with and without alcohol, a high cholesterol group without alcohol, and a low cholesterol/high carbohydrate group would have added considerably to your study. If data from these additional groups support your observations, the conclusions you have drawn would be even more secure.

In reviewing the manuscript, I was also looking for other data. For example, do you have data from hepatic bile on biliary lipids, calcium, or bilirubin? With those data you could speculate as to whether the changes that you have observed are occurring in the gallbladder or in the liver. Also, do you have data on serum bilirubin and calcium? With this information, you might be able to state whether there were differences in intestinal absorption. You did provide data on serum cholesterol, which was lower in the animals receiving ethanol. In the discussion of your paper, however, you suggested that ethanol was not affecting cholesterol absorption. How, then, do you explain the lower serum cholesterols in the ethanol-fed animals?

I was also looking for the gallbladder volumes of the two study groups. You reported hepatic bile volumes and stated that their differences were not statistically different. Frequently, when the gallbladders of these animals become filled with stone and crystals, the gallbladder volume may change. Were the gallbladder volumes different in your two study groups? Finally, your own very elegant work has demonstrated that ethanol can cause hemolysis. With hemolysis, biliary levels of bilirubin should be increased. How, therefore, do you reconcile your previous observations with the present study in which biliary bilirubin levels were similar in the two study groups?

DR. FRANK G. MOODY (Houston, Texas): Dr. Schwesinger and his colleagues are to be commended for looking at a very important issue: the prevention of gallstones. Very soon we are going to have a large population of patients in which, for surgeons, this is going to be an important issue.

There are many alternatives to cholecystectomy currently being touted, and soon you will read about the German trial where over 160 patients were treated by extracorporeal shock wave lithotripsy with bile salt adjuvant therapy. You will be surprised to learn that 100% of those treated in this way during the course of a year were rendered free of their presumed cholesterol gallstones.

In addition, percutaneous techniques are being developed which employ mechanical lithotripsy or dissolution by methyl-tert-butyl-ether. Furthermore, stones can be fragmented within the common duct by extracorporeal shock wave or direct mechanical lithotripsy. And the newest technique, tunable dye laser lithotripsy, is proving to be effective and safe. These advances will no doubt rapidly transform our approach to the treatment of gallstones.

DR. JAMES PATRICK O'LEARY (Dallas, Texas): I would like to compliment Dr. Schwesinger on his paper and to thank him for allowing me to read it ahead of time. I commend it to your perusal when it is in its final published form.

I would like to ask several questions. The serum cholesterol levels were low. Lower in the ethanol group than in the control group. Bile cholesterol was also low.

That raises the question: Are we dealing with a problem of absorption? Where is the cholesterol going? This gets back to the way the diet was constructed. If you were putting the alcohol with the cholesterol in the diet, then perhaps we have some local effect in the gut lumen that might be impacting on cholesterol absorption. Therefore, the animals may not be challenged with quite the same amount of cholesterol.

Do these animals conjugate their bile salt with taurine. In humans, about 80% of bile salts are with conjugated glycine. If the percentage of conjugation is different, would this make a difference in the study?

My third question has to do with the histology of both the gallbladder wall and the liver. I suspect that you looked at both of these and I was wondering if cholecystitis or changes in hepatic architecture were present.

DR. WILLIAM CHEADLE (Louisville, Kentucky): I, too, would like to compliment the authors on a very elegant and clinically relevant study in an appropriate model with proper analytic methods. It is certainly interesting that pigment stones account primarily for the probable increased incidence of gallstones in cirrhotic patients; however, ingestion of moderate amounts of alcohol seem to be protective against cholesterol stone formation.

Dihydroxy bile acids such as taurochenodeoxycholic acid have been shown to have a detergent effect on hepatocytes which can cause feathery hepatocyte degeneration. The increase in the dihydroxy to trihydroxy bile acid ratio seen in these animals, therefore, might eventually cause low-grade chronic hepatotoxicity. Have you examined liver tissue histologically in this model or others, and have you analyzed common duct bile acid composition which might be different from gallbladder bile and more indicative of that which is in contact with the hepatocytes?

DR. GORDON L. HYDE (Lexington, Kentucky): I, too, would like to welcome the authors to the Southern Surgical Association and commend their work.

I do question how this applies to human physiology and have some concerns that this paper will be misinterpreted by many to mean that drinking alcohol is good for you and will prevent gallstones.

You touched on the fact that the study was performed in dogs; are we certain that species differences might not account for the findings?

Secondly, according to my calculations, ethanol provided 35% of the total caloric needs of these animals which would equate to six to eight drinks a day for a 3-month period, hardly a normal alcoholic intake. Is this a dose-related phenomenon?

Thirdly, the duration of the experiment was only for 3 months. We know that alcohol has a salutary effect on triglyceride metabolism in moderate doses, but has a serious adverse effect in long-term use. Might this possibly apply to cholesterol metabolism in the long-term model?

I can share with you that, as an alcoholic myself, I used the triglyceride information as a rationalization to drink, and thought that if a little bit was good for your blood vessels, then a lot should be even better! Being in recovery now for many years, I have had many friends relapse, misinterpreting data such as this and using it as an excuse to drink.

The drug alcohol has serious adverse effects in 10% of the population. In this group it can be fatal and certainly a far worse illness than cholelithiasis. Let us be aware of the effect of this drug on the whole patient. For most of you, this is no problem, but for some of us, it is serious.

Until the evidence if solid, please be aware that this kind of information can have an adverse effect on thousands of our alcoholic patients.

DR. LESTER WILLIAMS (Nashville, Tennessee): I had not planned to discuss this paper, but the authors' suggestion concerning mechanism leads me to ask two questions. Each has been suggested by others.

Was there anemia? As you know, in the prairie dog with the carbohydrate diet, when there is anemia, this changes the mechanism by which these animals get their stones, and changes the nature of the stones which they get.

The second one is based on an observation of a number of years ago. When we used alcohol as a vehicle for one of our medicines and did not pay attention to total alcohol dose, our animals didn't do well. In those animals, because the liver was histologically bad, it handled cholesterol differently. I wonder what evidence you have about the liver in these animals.

DR. WAYNE H. SCHWESINGER (Closing discussion): I would like to thank all the discussants for their insightful questions and their thoughtful comments.

Dr. Pitt, I would certainly agree that we need to be looking at the possibility of enrolling other control groups. It was not until the end of the experiment and on careful reflection on the calcium data that we recognized that we may have selected as a control, and I think a necessary control, one that induced its own abnormalities. It would be appropriate, of course, to do a four-way study. The limitations of space and money have prohibited that approach, and we have had to stagger some of these experiments. I think we will need in the future to do other types of controls to solve the questions about calcium changes.

We did make an effort to collect hepatic bile, but due to technical problems in several animals in both groups, the collections of hepatic bile were insufficient to allow us to do complete determinations. In fact, the small sample size explains why the standard error was so large that we could not show statistical significance in terms of volumes. What I *can* say is that based on limited evidence in that experiment there was no qualitative difference in the lipid composition of hepatic bile as compared to gallbladder bile. There were quantitative differences, of course, in terms of concentrations, a reflection of the ability of the gallbladder to concentrate the lipids many times. So far as we could tell on this limited data, there were no major differences in the distribution of the cholesterol bile acids or phospholipids.

We have, in the past, demonstrated that ethanol administration is, in a variety of animal models, associated with intravascular hemolysis and increases in bilirubin in the hepatic and gallbladder bile. In our hands, however, those experiments require the intravenous administration of ethanol. When we administered ethanol orally, the hemolysis disappeared, so that the data we have in the current study does not contrast with the data that we have presented before related to hemolysis.

I am aware that in other animal models, hemolysis is thought to occur secondary even to oral ingestion. In particular, in the rat experiments done by Lieber there has been some evidence of increased unconjugated bilirubin in bile following ingestion of alcohol. That did not appear to be the case here, and these animals (to answer another question) were not anemic as compared with the control animals.

I appreciate Dr. Moody's underscoring of the importance of developments in the field of fragmentation of cholesterol stones by lithotripsy. I think that one of the things on the horizon facing general surgeons is the fact that many patients with asymptomatic gallbladder disease will be treated with the lithotriptor and then maintained on some type of chenolytic agent. I am not suggesting that alcohol be that agent, but it does give us some physiologic information about the kinds of substances that can cause a reduction in the cholesterol saturation index.

I am interested to hear that ethanol improves evacuation of the gallbladder in animals. Whether ethanol influenced gallbladder motility has been studied in humans before, and to my knowledge, was not the case. In experimental animals with better control, one might be demonstrating an important factor in the management of cholesterol gallstones. Nonetheless, one cannot overlook the fact that in the ethanol-treated animals, the predominant biologic change was the reduction of the cholesterol saturation index. It may be that a number of factors are responsible for this reduction in the incidence of stones.

Dr. Moody asked what would be an equivalent amount of Scotch? We plotted it out on the basis of the animals that we were dealing with and found that one would really have to drink probably half a bottle of Scotch or more to keep up with most of the animals. It is not the usual social dose of alcohol! We selected this dose because it is a dose that is typically used in research with rodents with alcohol and liquid diets. 35 to 37% is the level that is recommended for studies of the induction of enzyme systems and minimal changes in liver histology.

If I may have Slide No.30, I will demonstrate some of the changes that we see in liver histology. (Slide) We did obtain, of course, liver and gallbladder specimens, and what we saw was a range of changes. In this animal in the alcohol group, the liver histology was preserved normally. In contrast, in one of the other ethanol-fed animals, a moderate degree of lipid within the hepatocytes was documented. In a single animal, in the ethanol group, we actually see some periportal inflammation. No scar formation, however, and no necrosis was noted in any of the histologic specimens. Of interest, while we tried to rank the various changes in control and alcohol animals, the control animals had mild degree of fat in their liver as well, so it was impossible for us to demonstrate a statistically significant difference in histology.

Concerning the toxicity of dihydroxy bile acids as detergents that can affect hepatocytes: I would agree that is a possibility and has been documented even in patients receiving chenodeoxycholic acid for dissolution. However, again as was demonstrated in the liver slides that we reviewed, we found no necrosis or any severe evidence of damage.

Dr. Hyde, I certainly would accept the caveats which you raised about this topic, and I would be irresponsible if I should allow myself to be misinterpreted as suggesting that alcohol deserves to be used to prevent gallstones. I hope that the manuscript is clear in avoiding that conclusion. Certainly the doses we are talking about, as I have explained, were selected because they have been used by other investigators. Other lower doses will be used. I am, of course, not an advocate of irresponsible behavior for myself or others, and I think one does need to use caution when submitting this type of work. Thank you for bringing our attention to that concern.

There are, I am sure, many other questions. I think I have answered most. I greatly appreciated the opportunity to present this material.

Intraoperative Radiotherapy for Patients with Carcinoma of the Pancreas

The Howard University Hospital Experience, 1978–1986

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During the period from 1978 to 1986, 106 patients were diagnosed with carcinoma of the pancreas; 30 of these patients were excluded from this study. Of the remaining 76 patients, 40 did not receive intraoperative radiotherapy (IORT) and were used as the nonrandomized control group for the 36 patients who did receive IORT after histologic confirmation of carcinoma of the pancreas. The records of 35 patients were available for review. The group receiving IORT ranged in ages from 43 to 89 years (20 males and 15 females). Seventeen patients had distant metastatic disease. The primary was located in the head of the pancreas in 32 and the body in three. No patient in this group had a curative resection. All patients were treated by a combination of biliary and gastric bypass prior to or concurrent with IORT. IORT was begun only after obtaining a histologic diagnosis and prior to the completion of any anastomosis. Necrotizing pancreatitis occurred in the treated group. There was no statistically significant difference in the survival of the nonrandomized control and treated groups.

From the Departments of Radiotherapy and Surgery, Howard University Hospital, Washington, DC

CARCINOMA of the pancreas is the fifth leading cause of death from cancer in the United States. Several centers are now using intraoperative radiotherapy (IORT) in patients with localized, nonresectable carcinoma of the pancreas to provide a boost dose directly to the tumor in an attempt to increase survival. IORT has been incorporated with several other treatment modalities including chemotherapy, surgical procedures (resection or bypass), external beam radiation therapy, and sensitizers. The safety of such treatment has been demonstrated. Except for the results reported from the Massachusetts General Hospital adding misonidazole to IORT and external beam therapy,[1,2] the median survival of those having received IORT has been 8.8–12 months. The paucity of major complications in recently treated patients coupled with apparent retardation of local disease and demonstrable necrosis of the tumor in the pancreas suggests that this treatment modality has value in some patients. The records of all patients at the authors' institution diagnosed as having carcinoma of the pancreas from 1978 to 1986 were reviewed. The treatment results are reported for those patients who received IORT with bypass procedures alone or in combination with iodine 125 implantation, external beam radiotherapy, chemotherapy, and/or intraoperative hyperthermia.

Materials and Methods

From 1978 to 1986, 106 patients were diagnosed as having carcinoma of the pancreas. In 19 patients the diagnosis was made on clinical grounds without histologic confirmation. Eleven had been diagnosed and treated at other medical centers and were admitted to the authors' institution in a moribund condition. These 30 patients were excluded from this study. Of the remaining 76 evaluable patients, 40 did not receive IORT and were used as a nonrandomized control group for the 36 patients who did receive IORT with 35 of the latter records available for review.

The control group included 15 patients who were diagnosed but not treated, one patient who had a curative pancreaticoduodenal resection, 20 patients who had gastric and biliary bypass only, three patients who received bypass and external beam therapy, and one patient who received bypass and iodine 125 implantation. Patients in this group did not receive IORT because of the following: (1) inability to confirm the diagnosis on frozen section; (2) inability to isolate the tumor from surrounding structures; (3) bulky distant metastatic disease; (4) death occurring prior to the treatment date; and

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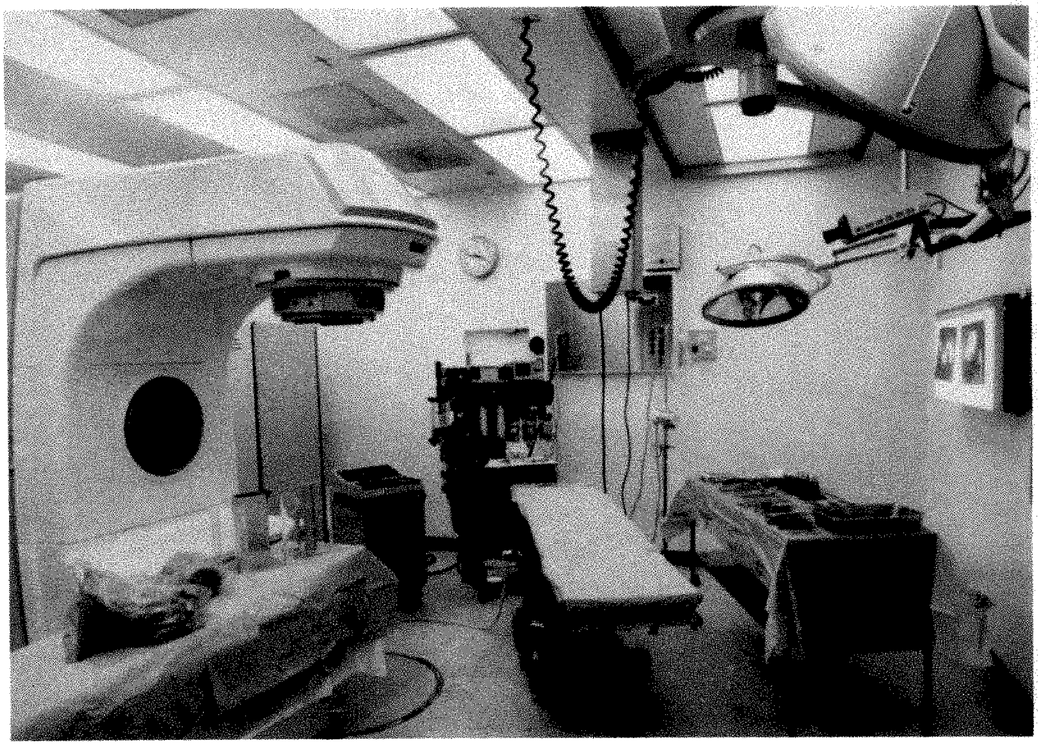

FIG. 1. The Howard University Hospital Intraoperative Radiotherapy suite consists of a standard operating room combined with a Clinac 18 Linear Accelerator, which can deliver electron beams of 6, 9, 12, 15, or 18 meV.

(5) patient refusal. Patients ranged in age from 36 to 92 years (average: 66.9 years) and included 16 males and 24 females. Twenty-six patients reported weight loss ranging from 8 to 65 lb (average: 24 lb). Twenty-one patients had distant metastatic disease on presentation and the primary was in the head in 38 and body and tail in two.

The 35 patients receiving IORT ranged in age from 43 to 89 years and included 20 males and 15 females. The duration of symptoms prior to the institution of therapy ranged from 2 weeks to 13 months. Twenty-one patients on presentation reported weight loss that ranged from 15 to 70 lb (average: 31.6 lb). Symptoms and physical findings were similar to those reported in other series. Seventeen patients had distant metastatic disease found at operation with the primary located in the head of the pancreas in 32 and the body in three. Twelve patients with distant metastases were treated during the Phase I toxicity study to determine side effects and complications of IORT.[3] No patients treated with IORT had bulky distant metastases. All patients had nonresectable lesions. Preoperative and postoperative enteral and parenteral hyperalimentation was liberally utilized.

Patients were administered general anesthesia in a special IORT suite and prepped and draped in the usual manner (Fig. 1).[4] Surgery and radiotherapy were initiated and terminated in the suite; patient transportation was not required. To achieve maximal visualization for both exploration and IORT, a bilateral subcostal surgical incision was usually employed. Once the tumor was exposed and staged, a wedge biopsy or preferably a transduodenal needle biopsy was performed to obtain frozen section confirmation of the diagnosis. No attempts were made for partial or total resection of the primary. The appropriate electron beam energy and specific applicator (collimator) size, which allowed for at least a 1–2 cm margin of normal tissue, were assessed by palpation and direct measurement of the visualized tumor.

The normal uninvolved intra-abdominal structures were then retracted from the treatment field while the applicator was placed down over the tumor. The transparent acrylic (Lucite) portion of the applicator, which is in contact with the tumor surface, permits direct viewing of the radiation field through its sides, and at the same time restrains the uninvolved bowel outside of the direct radiation port (Fig. 2).

All treatments were given with electron beams with energies of 9, 12, 15, or 18 meV, with 80–90% depth dose distributions of 3, 4, and 5 cm. The rapid and sharp fall-off in depth dose of electrons is attractive for the intraoperative technique because it limits the exit dose to normal structures, such as the spinal cord, which lies posterior to the tumor. Circular treatment cones of 6.0, 7.5, 8.5, and 9.6 cm in diameter were used to treat the pancreatic lesions. These cones were adequate in treating the well-circumscribed lesions of the pancreas; however, given the multicentricity of many pancreatic malignancies, larger cones of probable rectangular shape may be more efficacious when one considers treating the whole pancreas by the intraoperative technique. Step-

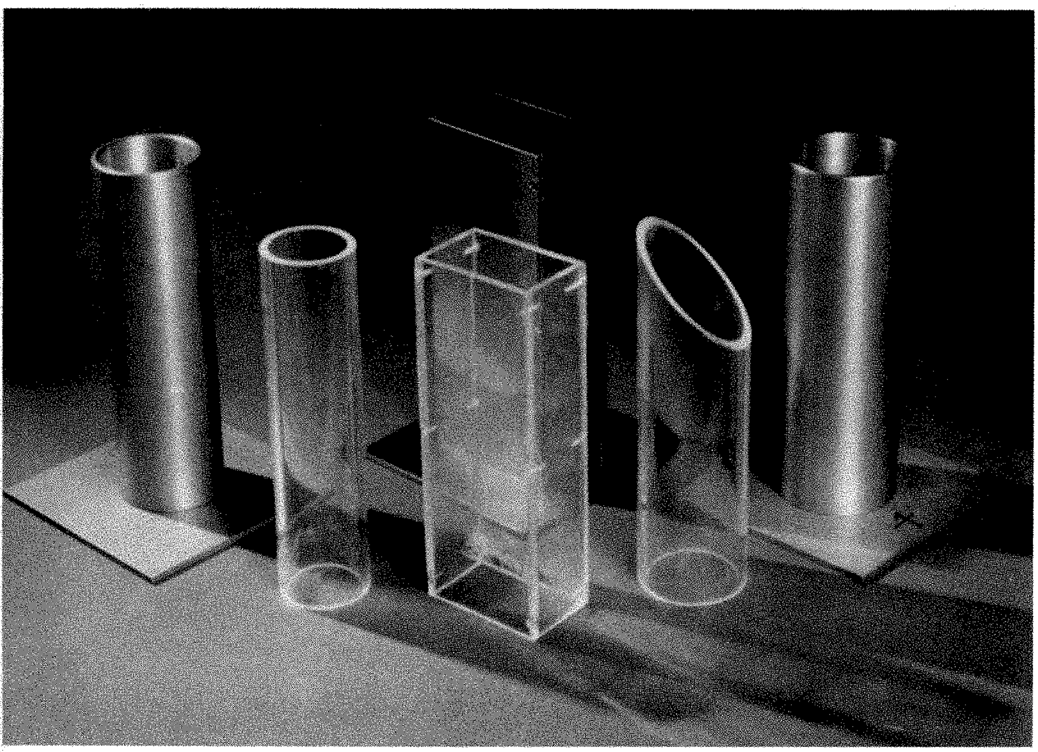

FIG. 2. These represent special electron beam collimators for IORT. The outer part is made of aluminum and is attached to the head of the accelerator; the inner part is made of acrylic and can telescope into the outer aluminum part.

wise decremental doses from 3000, 2500, 2000, and 1500 cGy were given in single doses in the Phase I study. The remaining patients received 2500 cGy as a boost dose plus fractionated external beam photons (usually 4000–4500 cGy). The irradiated volumes, which included the pancreas, its regional lymph nodes, and portions of the duodenum, varied from 30 to 180 cm^3.

During the interval of irradiation all members of the surgical team left the surgical radiotherapeutic suite. The patients' vital signs were monitored remotely via an oscilloscope mounted just above the treatment console control panel. Additional monitoring was achieved indirectly through a mirror system and the television camera mounted on the wall inside the treatment room.

Biliary and gastric diverting procedures were performed after completion of the IORT to avoid further operative trauma and irradiation to new anastomoses. After closure of the surgical wound, patients were transported to the surgical intensive care unit for observation. No special radiotherapy precautions were indicated.

TABLE 1. *Number of Patients Treated, Presence or Absence of Distant Metastases, and Survival Rates*

No. of Patients	Metastases*	Treatment IORT +	Survival (mo)
21	13	Bypass only	6.2
6	3	External beam	8.8
5	0	External beam and iodine 125	8.2
2	1	External beam and chemotherapy	6.7
1	0	External beam and IOHT	22

* Distant metastases did not alter survival.

Therapy and Results

IORT was given in various combinations including (1) bypass only; (2) bypass and external beam therapy; (3) bypass, external beam, and iodine 125 implantation; (4) bypass, chemotherapy, and external beam therapy; and (5) bypass, external beam, and intraoperative hyperthermia (IOHT). These data including survival rates are outlined in Table 1.

One patient was a 56-year-old man who received simultaneous IORT (2500 cGy) and IOHT (43–44 C for 40 minutes) with additional postoperative fractionated external beam irradiation (2000 cGy). Postoperatively, the patient complained of persistent midepigastric pain ultimately requiring implantation of a morphine pump. He survived for 22 months with good quality of life until his last 2 weeks. He died of massive upper gastrointestinal hemorrhage. Results of an autopsy are pending.

Only one patient in the series was still alive functioning fairly well but with progressive disease 11 months after treatment with IORT, chemotherapy, and external beam. Fifty seven per cent of patients receiving IORT had significant relief of abdominal pain within 1–2 weeks after treatment. In a nonrandomized control group of 40 patients treated with varying modalities, the survival rate was 5.4 months.

Metastases

Of the five aforementioned treatment groups, no liver or other distant metastases were present in the five patients treated with iodine implantation or in the one patient treated with hyperthermia. One of two patients treated with chemotherapy had liver metastases as did three of six treated with external beam and 13 of 21 treated with IORT alone (Table 1). There was no statistically significant difference in survival in patients with or without distant metastases.

Complications

During the Phase I study involving 19 patients, there were three perioperative deaths and three late complications. The complications were: (1) massive upper gastrointestinal hemorrhage from erosion into the superior mesenteric artery resulting in the death of a 65-year-old male 6.5 months after IORT; (2) posterior gastric wall ulcer in a 73-year-old patient who expired 3 months after treatment with massive tumor necrosis; and (3) ascending cholangitis and common bile duct stricture in a 52-year-old patient who died 3 months after treatment. All three patients had treatment volumes greater than 100 cm.^{3} Two patients received 3000 cGy and one received 2000 cGy. The three perioperative deaths in this group were intraoperative cerebrovascular accident, postoperative hemorrhage secondary to needle biopsy injury to vascular structures, and hepatorenal syndrome and aspiration in a patient with poor liver function. Of the remaining 16 patients, two developed necrotizing pancreatitis and pancreatic abscess: a 72-year-old man treated with IORT and external beam therapy who expired 2 months after treatment and a 56-year-old woman treated with IORT and iodine 125 implantation who died 5 months after treatment. Both had open wedge biopsy because transduodenal biopsy was inconclusive.

There was no delayed wound healing. Relatively minor complications included two patients with gastritis and seven patients with prolonged gastric atony in whom portions of the stomach and duodenum were included in the radiation field. Autopsies obtained on eight patients revealed massive tumor necrosis, mild fibrosis, and islands of viable cancer.

Discussion

There has been continuing interest in the role of IORT for pancreatic cancer since Abe and Takahasi introduced this modality in 1964.[5] Howard University Hospital in 1976 was the first institution in the United States to use IORT and began its Phase I study for carcinoma of the pancreas in 1978. The most recent report from Abe et al. suggested that IORT in combination with external beam radiotherapy may improve survival in pancreatic cancer.[6] They reported the results of 110 patients with locally advanced disease who were entered into the pilot study.[6] Forty-nine patients were treated by IORT alone (Group 1), 20 patients were treated by IORT followed by external beam radiotherapy (Group 2), and 41 patients were treated by operation alone (Group 3). The IORT dose for patients treated by IORT without external beam irradiation ranged from 3500 to 5500 rads depending on the residual tumor volume and tumor site. For those who were treated by IORT plus external beam irradiation, the IORT dose was 1000–2500 cGy, whereas external beam radiation started 3–4 weeks after IORT had a dosage ranging from 3500 to 5500 cGy with an average of 4000 cGy. The median survivals were 5.5 months for Group 1, 12.0 months for Group 2, and 5.5 months for Group 3. About 70% of their patients who complained of severe abdominal or back pain experienced relief within a week after IORT while 57% of these patients had relief within 1–2 weeks. Approximately 30% of their patients with pancreatic head cancer who received an IORT dose of more than 2500 cGy experienced diarrhea and/or bloody stool and about 10% developed duodenal ulcers. Other complications included prepyloric obstruction in one patient, death probably secondary to acute pancreatic necrosis in another patient, and two patients with delayed gastrointestinal tract bleeding. The most encouraging results for this difficult clinical problem have been reported by groups using intraoperative radiotherapy as a boost in external beam radiotherapy. The advantages of a combined IORT and external beam treatment are as follows: (1) it is difficult to eliminate a bulky tumor by a single IORT dose; (2) a higher dose can be delivered to tumors by external beam plus IORT boost with less risk of adjacent normal tissue necrosis; and (3) the risk of marginal recurrence may be decreased by external beam irradiation.[6,7]

The results of early clinical work from Japan, which were partly supported by experimental animal studies suggested there were few long-term complications to retroperitoneal structures from IORT.[5] The acute and late responses of normal canine tissues to large single doses of electron radiation indicated that the major retroperitoneal blood vessels, which were most frequently and unavoidably irradiated, had a high tolerance, while the hollow viscera and solid organs were more sensitive than retroperitoneal structures. In the abdominal solid organs, doses between 2000 and 3000 cGy, in general, led to moderate inflammation, cellular atrophy, and fibrosis. Partial irradiation of the duodenum with doses of 2000–4500 cGy resulted in duodenal narrowing, but as long as the total circumference was not irradiated or the loop of intestine was nonfunctional, stenosis was minimized. Safe clinical practice based on these studies, however, nearly always requires surgical bypass of the biliary or gastrointestinal tract if any portion of these organs receive any IORT dose.[8,9]

Dobelbower et al.,[10] Shipley et al.,[11] and Syed et al.[12] reported median survival times of 11–15 months in patients treated with combination interstitial iodine 125 implant and external irradiation. Rich[13] reported that radiation therapy for 41 patients with unresectable pancreatic cancer resulted in a median survival of 7 months. There was no difference in median survival for patients receiving external beam alone, IORT plus external beam, or gold 198 implant with or without external beam irradiation.[13]

Wood et al. reported 12 patients treated with external photon beam and intraoperative electron beam irradiation who had a median survival of 15 months or more.[14] This survival rate is contrasted with 12 months for patients treated with iodine 125 seeds as boost irradiation and less than 10 months for patients with unresectable disease treated by external beam irradiation and chemotherapy by the Gastrointestinal Tumor Study Group. Six of the 12 patients received chemotherapy. The combination of tailored external beam irradiation and intraoperative boost provided an average tumor dose of 6225 cGy, which is the biologic equivalent of 8700 cGy of conventionally fractionated radiation therapy. Complications occurred in all three patients who had the distal stomach and pylorus included in the intraoperative irradiation field—gastric outlet obstruction, pancreatic abscess, and suture line leak.

Shipley et al.[2] reported the results of 29 patients treated by electron beam IORT plus conventional external beam radiation therapy. Adjuvant chemotherapy (FAM—5 fluorouracil, adriamycin, and mitomycin-C) was given to 23 of the 29 patients while the last 13 patients in the series also received intravenous (I.V.) misonidazole, a drug that sensitizes hypoxic cells to radiation. Their median survival was 16.5 months. Studies with misonidazole are continuing, but these investigators believe that the continued use of misonidazole in this setting is not warranted.[1]

Gunderson et al.[15] reported a similar median survival time of 11–12 months for patients treated with IORT plus external beam irradiation or external beam therapy alone. Fifty-two patients were treated with an IORT dose of 1750 cGy (two patients) or 2000 cGy (50 patients) plus 4500–5000 cGy of fractionated external beam irradiation. They have begun a Phase II pilot trial, which combines upper or total abdominal irradiation and infusion of 5-fluorouracil with tumor nodal irradiation plus IORT to evaluate tolerance and the relative incidence of abdominal failures.[16]

Because of these laboratory studies and the results with the one patient treated with simultaneous IORT and intraoperative hyperthermia followed by external beam therapy, the authors have begun a study using a combination of these modalities.[17] This therapeutic approach has not been used previously for nonresectable pancreatic cancer. The rationale for hyperthermia in cancer therapy is based on various biologic effects that have been confirmed in many *in vitro* and *in vivo* studies: (1) hyperthermia kills cells exponentially as a function of time and temperature at or above 43 C; (2) hyperthermia selectively kills S-phase and other radioresistant cells, such as hypoxic tumor cells, acidic cells, and nutritionally deprived cells; (3) hyperthermia not only complements but also acts synergistically with ionizing radiation by inhibiting DNA repair by heat shock proteins or by interacting with cellular membrane structures; and (4) hyperthermia interacts synergistically with cytotoxic agents and can overcome some kinds of drug resistance by various mechanisms, *e.g.*, increasing intracellular drug uptake, inhibiting repair mechanisms, and increasing drug activity. Clinical trials using radiation therapy and adjuvant hyperthermia compared with radiation therapy alone have demonstrated an improvement in partial and complete response rates with the addition of hyperthermia. Overall complete response rates for radiation alone are 30–40% compared with 70–80% for the combined modality approach.[18-21]

Conclusion

Although IORT has been used for over 50 years, there is now renewed enthusiasm especially with the use of electron beam techniques, which have improved the ability to deliver high intraoperative radiation doses safely. The number of patients in this series is too small to render any definite conclusions. Fifty-seven per cent of these patients had significant relief of severe abdominal and back pain. There was no statistically significant difference in survival whether or not patients were treated with IORT. Nevertheless, with the dismal outlook for patients with cancer of the pancreas, further studies with IORT appear warranted.

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DISCUSSION

DR. J. SHELTON HORSLEY III (Richmond, Virginia): It is a pleasure to welcome LaSalle Leffall to membership in the Southern Surgical Association and congratulate him on this excellent presentation.

We have followed the work that Howard University has done in intraoperative radiation therapy. They have been at the forefront of this very interesting field. We do not have this capacity at the Medical College of Virginia, so we have no personal experience.

Dr. Leffall has outlined the pitfalls and very objectively analyzed his results. I am glad he is moving forward in this field, because I think it does have something to offer in selected areas. People with the expertise and facilities to do this should continue with this investigational type of therapeutic approach.

I think one of the exciting things about this work is the pain control. As he pointed out, 57% of his patients got pain control within 1 to 2 weeks. The Japanese experience is some 70%. Pain control is a truly positive result in patients with carcinoma of the pancreas.

I also call to your attention that this has been utilized in other areas of the gastrointestinal tract. The Massachusetts General Hospital and the Mayo Clinic have utilized pain control with rectal carcinoma, and their results, utilizing preoperative radiation therapy followed by resection and intraoperative radiation therapy, have actually shown a significant improvement in survival and decrease in local recurrence, as compared to preoperative radiation and surgical resection.

I would like to ask Dr. Leffall: Does he think there is a place for intraoperative radiation therapy following pancreatic resection, such as a Whipple operation, for carcinoma of the head of the pancreas?

We will follow this work with great interest, and we wish him well.

DR. HARRIS B. SHUMACKER (Bethesda, Maryland): It is a great pleasure for me to listen to LaSalle Leffall present this new work. He knows in what high regard I hold him and how much my colleagues and I in Bethesda enjoy his frequent visits to Walter Reed Army Medical Center as the person in charge of grand rounds.

The other day when I was trying to straighten out my continually disordered office, I ran across a four-line letter from Ronald Malt of the Massachusetts General addressed to Ian Munro, Editor of the Lancet. It says:

"Perhaps the author of your 'Intraoperative Radiotherapy' (10 December 1983) might want to know that between 1937 and 1942, Leo Eloesser of San Francisco . . . started a series of radiation of 300–400 Roentgens through the open mastectomy wound for breast cancer."

His reference is to the biography of Leo Eloesser, subtitled "Eulogy for a Free Spirit," which I wrote some years ago now. (I am not trying to sell my biography, but I do recommend it.)

While I do not think that in preparing a paper it is necessary to go beyond the medical literature and read every biography written for information of the past, I knew that LaSalle, being the scholar that he is, would have covered the past contributions in this particular area. Dr. Eloesser's work at the San Francisco County Hospital was not published because the results were not very conclusive and because prior publications were known to him.

I mention his work to point out the splendid opportunity we have had in 1987 and the preceding years to do with ease things that were so cumbersome a few years ago.

Leo Eloesser, his associates, and his residents have told me how laborious it was to try to pick a patient up from the operating table of the old County Hospital and maintain some semblance of sterility, then place the patient on a stretcher, carry the patient out of the operating room and down the hallway to a rickety old elevator in the *next* hallway, down the elevator to the therapy department, and then reverse the entire procedure. With what ease LaSalle can accomplish all of this in the operating rooms at Howard University!

Mr. President, may I make an entirely irrelevant comment? (Actually, it is not entirely irrelevant, since this meeting began with those beautiful audiovisually recorded words of welcome and congratulations from our President and Mrs. Reagan.)

A few years ago, when it was necessary for President Reagan to have a colectomy for what appeared to be, from all preoperative studies, a favorable lesion of the cecum it was felt necessary at that time to have a surgical oncological observer on hand. Had I had the right to decide whether this was necessary or not, I would have made the decision that it was not. I knew that the President's operation was in good hands, that it would go as uneventfully as it did; but had I decided that it was necessary to have an oncological specialist standing by, I would have selected from the neighborhood Dr. LaSalle Leffall, and that would have had one very beneficial effect. We wouldn't have seen the same face on television so often. In fact, I am sure we wouldn't have seen a face at all on television, nor would we have heard so many comments, both relevant and irrelevant, about what took place on that historic date, for Dr. Leffall would surely have remained as quietly in the background as did the Chief of Surgery at the Navy Hospital, Dale Oller, who operated on our president so skillfully. It would have perhaps had an *adverse* effect in that it would have made those who are so antagonistic to everything that happens in the White House even more antagonistic than they were and are, but it might have also had one other bad effect. It might have delayed the current managment of dissemination of medical news about those in our First Family, which is now handled so beautifully by Colonel John Hutton.

At the present time, the correspondents are informed nicely but emphatically that they are not welcome at Navy Bethesda Hospital or any other place where the First Family might be treated. Still, they are welcome around the White House, where concise and well prepared handouts will frequently be available to them, describing not only what treatment has been given, but what is on-going. This has worked out very well and has saved our President, and especially his First Lady, a great deal of agonizing discomfort.

LaSalle, we congratulate you on a very interesting study. There is only one thing that I would like to ask. I have the impression that, 8 or 10 years ago, the combination of external radiation with general body hyperthermia did not work out to be any panacea for the treatment of adenocarcinoma, and I wonder whether localized hyperpyrexia and intensive local radiation would have a different effect.

DR. KIRK MARTIN (Jacksonville, Florida): I would like to congratulate Dr. Leffall and to express my appreciation for his allowing me to review his excellent, detailed manuscript.

We are indebted to him for his early pioneering work on intraoperative radiotherapy in the United States.

We became involved with intraoperative radiotherapy through an NCI contract in late 1980, and to date, we have used intraoperative radiation to treat 64 patients with locally unresectable pancreatic cancer, and an additional four with residual disease following pancreatectomy.

Last year, we compared our treatment of locally unresectable—that is, no distant metastases— ductal pancreatic carcinoma, and the results are very similar to the Howard experience that was so superbly presented.

Allow me to briefly summarize our findings and then ask Dr. Leffall a question.

Between 1981 and 1985 we treated 37 patients with an intraoperative radiation boost, generally 20 Gray using 18 Mev electrons, followed by 45 to 50 Gray external photon beam. We compared this to 122 patients treated by external beam radiation alone in doses ranging from 40 to 60 Gray. The patients were matched according to tumor characteristics and performance status.

There was no difference in survival between external beam alone and external beam plus intraoperative radiotherapy: 12.6 months and 13 months, respectively.

One-year and two-year survival was also similar, 55 *versus* 58% and 16.5 *versus* 12%.

Distant metastases occurred in equal numbers in both groups. Liver 40%; peritoneal seeding, 30%; lung, 20%. Multivariate analysis showed a significant difference only for local recurrence rates: 16% failure in the intraoperative *versus* 72% failure rate in the external beam alone group.

These data plus those of others led us largely to abandon intraoperative radiation therapy for unresectable pancreatic carcinoma. We have utilized celiac block for pain control.

While intraoperative electrons may be of significant value in other sites, such as residual colorectal cancers, I would like to ask Dr. Leffall if, until more effective systemic treatment is available, they still feel intraoperative radiation is justifiable in patients with unresectable pancreatic carcinoma.

DR. LLOYD M. NYHUS (Chicago, Illinois): I suppose you are all wondering why I rise to discuss this paper. The experience that we have had with intraoperative manipulation in cancer and other lesions of the pancreas with intraoperative ultrasound allows me to make a positive comment. But that is not the reason I rise.

You talked about the complication, a rather difficult one, of prolonged gastric atony. It seems to me that if there is a high incidence of this, you should consider the use of the new types of tubes where you can suck out the material in the stomach and at the same time give early small intestinal feeding.

Recently in our quality assurance program, we have reviewed the problems related to hyperalimentation. We have found an inordinate number of complications following the use of hyperalimentation as well as increased cost.

I would ask you, Dr. Leffall, to comment on the more routine use of this type of postoperative gastric decompression and jejunal feeding at an early time.

DR. ISIDORE COHN, JR. (New Orleans, Louisiana): I woul
congratulate Dr. Leffall for bringing into current surgical pe
the use of intraoperative radiotherapy for carcinoma of the
During the ten years that I had direction of the NCI's National
atic Cancer Project, we were looking, as was everyone else,
new method of controlling the disastrous disease that pancreat
is, and, obviously, one of the things we were thinking about a
to evaluate was the true place of this particular modality.

Dr. Leffall's co-author, Dr. Goldson, a very bright, young
sive, and enthusiastic radiotherapist, talked to us on several
about the results of this form of therapy, and we were never a
any one of the surgeons to tell us what they really thought a
think that now, with the review that we have heard this mor
have some better perspective of what the true place is of this p
modality related to pancreatic cancer.

I think that, while we need to continue to evaluate it, we
evaluate intraoperative radiotherapy against the background
we have heard this morning and what its real place might be
that is very important from a surgical standpoint.

DR. LASALLE D. LEFFALL, JR. (Closing discussion): First,
like to thank the fellows of the Southern Surgical Associatio
many letters, telegrams, and telephone calls I received last y
gaining admission to the Association. These acts of friendship
poignant reminders of what membership in this organizatio
sents. I would like to thank all of the discussants for their rem
will try to answer the questions that have been asked.

Dr. Horsley asked about the role of intraoperative therapy p
tive resection. Shelton, one of the real problems with that is n
We just don't have enough numbers to treat comparable gro
resection alone and with resection plus intraoperative x-ray t
will tell you what we do at Howard. All patients with resectab
and pancreatic cancer have potentially curative resections per
Even if all gross tumor is removed, we give adjuvant intrao
radiation therapy. The only trouble with this approach is that
measure whether it is effective or not. You can never come b
and see whether you did anything. So that is the problem you h
that.

Dr. Zeppa asked me a question as I sat down. What ab
needle aspiration biopsy? We have not used it. That is all I can
use it for breast cancer. Maybe we should begin using aspiratio
for cancer of the head of the pancreas. We have just not don
have either used the transduodenal tru-cut needle core biopsy
is unsuccessful, a wedge biopsy.

I want to thank Dr. Shumacker for his kind and thought
ments. There is no question that treatment with systemic hy
mia has been in the domain of the charlatan, as much as in the
of clinicians who have been trying to do something to trea
effectively. Further study of intraoperative hyperthermia and r
therapy is needed.

In terms of the question that Dr. Martin asked me, is intrao
radiation therapy still justifiable? We look with interest at w
are doing at the Mayo Clinic, even though Dr. Martin is now
my home-state of Florida, at Jacksonville, Mayo Clinic South.
still interested in their results because they have significant n
and we want to know whether they have shown any improve
the management of patients with nonresectable cancers of t
creas. Do we still think it is justifiable? Not in the ways it has b
in the past. That is the reason we have chosen to go with IO
intraoperative hyperthermia.

Dr. Nyhus, we have used enteral and parenteral hyperalim
very liberally. I know your question came from a disintereste
ased party, and that I understand. We do use the feeding jejun
but perhaps we do need to be a bit more aggressive in what we
as feeding tubes are concerned.

Finally, I would like to thank Dr. Isidore Cohn for his grea
us in the early phases of our work, when he was in charg
pancreatic cancer program funded by NIH.

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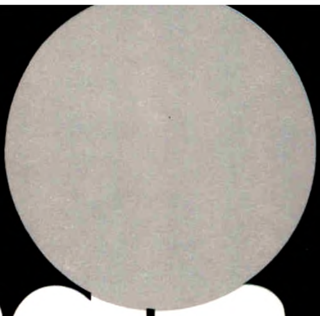

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In another comparative in vitro study, UNASYN "...was far more active than any of the cephalosporins tested against the *B. fragilis* group."[2]

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CEFOTETAN (n = 96)	55%
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S. epidermidis (n = 127)	**98%**
Enterococci[¶] (n = 86)	**98%**
Misc. streptococci[¶] (n = 57)	**91%**

In vitro studies have also demonstrated the susceptibility of *S. saprophyticus*, *S. viridans*, *Streptococcus pneumoniae*, and *S. pyogenes* to UNASYN.

UNASYN also possesses a practical spectrum of gram-negative activity, which includes pathogens such as ***Escherichia coli*** and ***Proteus mirabilis***.

[†] In vitro susceptibility does not necessarily imply a correlation with in vivo results.

[‡] Breakpoints listed in prescribing information: UNASYN, 16 μg/mL (reported as ampicillin concentration); metronidazole, 16 μg/mL; clindamycin, 4.8 μg/mL. Estimated breakpoint for chloramphenicol based on clinical experience, 16 μg/mL.

[§] Strains used and number of isolates tested were: *Bacteroides fragilis* group, 70; pigmented *Bacteroides* group, 22; other *Bacteroides* sp, 46; *Fusobacterium* sp, 32; *Clostridium difficile*, 19; other *Clostridium* sp, 33; nonsporeforming gram-positive rods, 23; gram-positive cocci, 36.

[||] Susceptibility breakpoints used: UNASYN, 16 μg/mL (expressed as ampicillin concentration); cefoxitin, cefotetan, and ceftizoxime, ≤32 μg/mL.

[¶] These non-β-lactamase-producing strains are susceptible to ampicillin alone.

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BRIEF SUMMARY

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INDICATIONS AND USAGE

UNASYN is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.

Skin and Skin Structure Infections caused by beta-lactamase producing strains of *Staphylococcus aureus, Escherichia coli,* Klebsiella* spp.* (including *K. pneumoniae*), Proteus mirabilis,* Bacteroides fragilis,* Enterobacter* spp.,* and *Acinetobacter calcoaceticus.**

Intra-Abdominal Infections caused by beta-lactamase producing strains of *Escherichia coli, Klebsiella* spp. (including *K. pneumoniae*), Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.*

Gynecological Infections caused by beta-lactamase producing strains of *Escherichia coli,** and *Bacteroides* spp.* (including *B. fragilis**).

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

While UNASYN is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.

CONTRAINDICATIONS

The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS

General: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN.

Drug/Laboratory Test Interactions: Administration of UNASYN will result in high urine concentration of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriolglucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with UNASYN.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy

Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See—Drug/Laboratory Test Interactions.)

Labor and Delivery: Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.

Pediatric Use: The efficacy and safety of UNASYN have not been established in infants and children under the age of 12.

ADVERSE REACTIONS

UNASYN is generally well tolerated. The following adverse reactions have been reported.

Local Adverse Reactions

Pain at IM injection site—16%
Pain at IV injection site—3%
Thrombophlebitis—3%

Systemic Adverse Reactions

The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.

Additional systemic reactions reported in less than 1% of the patients were: itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis and mucosal bleeding.

Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

Hepatic: Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.
Hematologic: Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.
Blood Chemistry: Decreased serum albumin and total proteins.
Renal: Increased BUN and creatinine.
Urinalysis: Presence of RBC's and hyaline casts in urine.

The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN.

Gastrointestinal: Gastritis, stomatitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity Reactions: Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin (see WARNINGS).

Hematologic: In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

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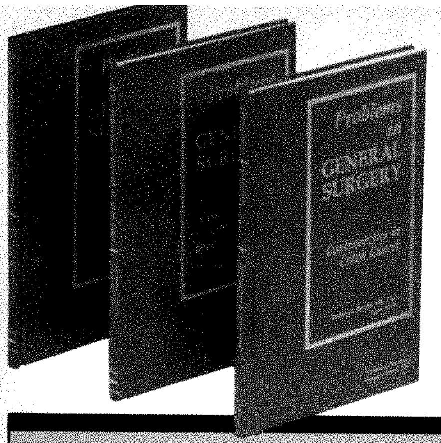

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Vol. 4, No. 1

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Vaterian Cancer in Siblings

JOHN C. AUSTIN, M.D., CLAUDE H. ORGAN, JR., M.D., F.A.C.S., G. RAINEY WILLIAMS, M.D., F.A.C.S.,
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The simultaneous occurrence of Vaterian carcinoma in two siblings suggests a genetic influence in their pathogenesis. Their classic clinical presentation of obstructive jaundice and weight loss required pancreaticoduodenectomy for this neoplasm. Pedigree analysis revealed a third sibling who died from an unresectable periampullary malignancy. Neither of the probands exhibited, as late as the seventh decade, evidence compatible with a diagnosis of familial polyposis coli or Gardner's syndrome. Flow cytometry studies revealed an aneuploid distribution in one tumor and tetraploid in the other. The rarity of this neoplasm, in the absence of contributing epidemiologic factors, suggests that this is a pleotrophic manifestation of a cancer-prone genotype.

CARCINOMA of the ampulla of Vater, a rare tumor of the duodenum, constitutes 0.01% of solid tumor cases and is found in 0.2% of postmortem examinations.[1] The overwhelming number of malignant ampullomas appear sporadically in the population and are considered to be multifactorial in origin and nonheritable. A previous report presented to this association in 1976[2] discussed the association of periampullary malignancies, Gardner's syndrome (GS), and familial polyposis coli (FPC). The simultaneous occurrence of this rare duodenal neoplasm in sibling males suggests a genetic influence on pathogenesis.

Case Reports

Case 1. A 66-year-old man presented to the hospital with a 3-week history of painless jaundice, dark urine, and a 6-month weight loss of 15 lb. He denied any previous history of hepatitis or pancreatitis, although a single-unit blood transfusion was received during an uncomplicated cholecystectomy 15 years prior to admission for cholelithiasis.

Past medical history was unremarkable except for moderate controlled hypertension. Medications included clonidine and a tricyclic antidepressant. Physical examination demonstrated a deeply jaundiced, emaciated man. Except for an enlarged liver, abdominal examination was unremarkable for tenderness or palpable masses.

Abnormal laboratory data included a total bilirubin of 15.5 mg/dL, alkaline phosphatase of 575 U/L, and an SGOT of 213 U/L (Table 1). Computed axial tomography (CAT) of the abdomen revealed a cystic mass in the head of the pancreas, dilated intrahepatic and extrahepatic bile ducts, and no significant periaortic lymph node enlargement (Fig. 1). Percutaneous transhepatic cholangiography confirmed the presence of gallstones plus intrahepatic and extrahepatic biliary duct dilatation secondary to a distal common duct obstruction. Diffuse enlargement of the pancreatic duct was demonstrated on endoscopic retrograde cholangiopancreatography (Fig. 1). Biopsy of a friable mass at the ampulla of Vater proved to be adenocarcinoma on frozen section.

At laparotomy a small mass was present in the head of the pancreas with no evidence of hepatic or lymph node metastases. Pancreaticoduodenectomy was performed uneventfully. The presence of a 2-cm ampullary adenocarcinoma was confirmed on microscopic examination; ten identifiable lymph nodes were free of tumor (Fig. 2). The patient was discharged on the 16th postoperative day following an uncomplicated course. Subsequent colonoscopy and barium enema, performed because of concern that the lesion might be associated with FPC, were both within normal limits with no evidence of gastrointestinal polyps. At 16 months there were no signs or symptoms of recurrent disease with normal nutrition. The patient expired 30 months after the operation. Postmortem examination was not obtained.

Case 2. A 64-year-old brother of Case 1 had always been in good health. Two weeks after his brother's operation he was admitted with similar symptoms, *i.e.,* a 2-month history of painless jaundice, dark urine, and a 22-lb weight loss. Hepatitis profile was HAV antibody and Hb core antibody positive; Hb surface antigen and IgM were negative (Table 1). There had been no previous serious illnesses, operations, or hospitalizations. On physical examination he was emaciated and icteric. Abdominal examination revealed an enlarged liver 12–13 cm wide at the midclavicular line. Abnormal laboratory values included a total bilirubin of 9.4 mg/dL, alkaline phosphatase of 410 U/L, SGOT of 239 U/L, and guaiac-positive stools (Table 1).

Presented at the 100th Anniversary Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 6–9, 1987.

Reprint requests and correspondence: Claude H. Organ, Jr., M.D., University of Oklahoma Health Sciences Center, Department of Surgery, P.O. Box 26307, Oklahoma City, OK 73126.

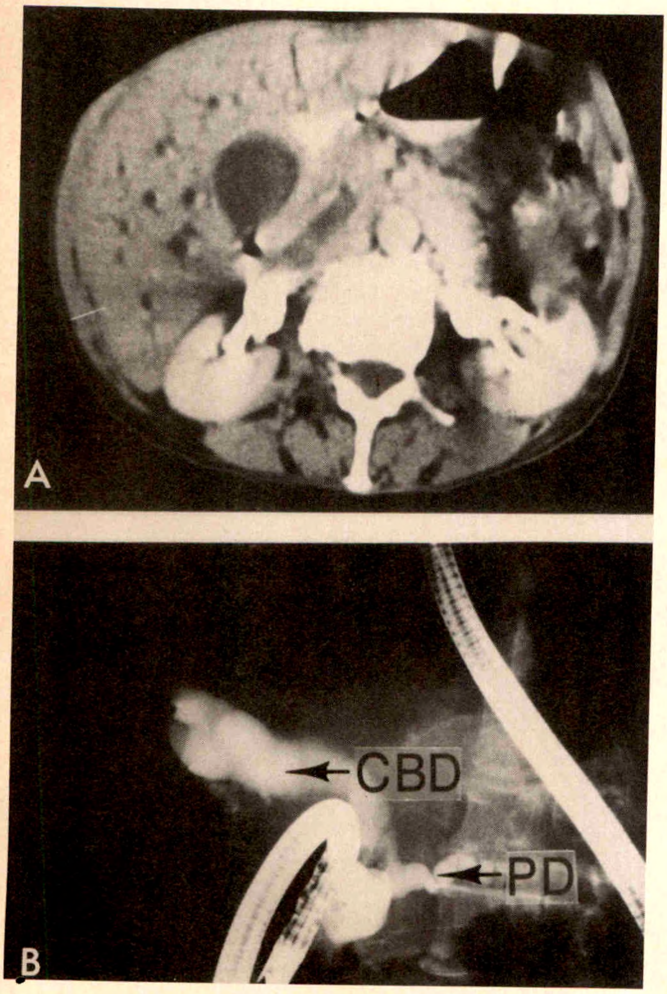
Submitted for publication: December 10, 1987.

TABLE 1. *Laboratory Determinations*

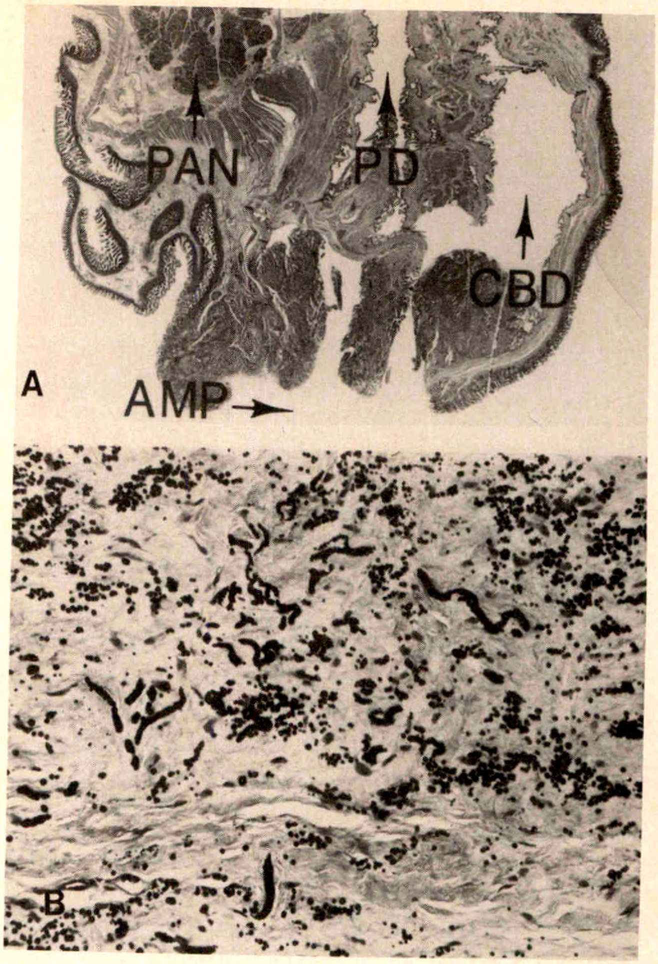
	Case 1	Case 2
Serum bilirubin	15.5	9.4
Alkaline phosphatase	575	410
SGOT	213	239
HAV antibody	Negative	Positive
Hb core antibody	Negative	Positive
Hb surface antibody	Negative	Negative
IgM	Negative	Negative

Ultrasonography of the pancreas and biliary tree demonstrated dilated intrahepatic and extrahepatic biliary ducts without evidence of cholelithiasis. An abdominal CT scan revealed no evidence of a pancreatic mass or periaortic–pericaval lymphadenopathy. On ERCP a friable fungating mass was observed at the ampulla of Vater and a dilated pancreatic duct was demonstrated (Fig. 3). Biopsy of the mass was compatible on light microscopy with a diagnosis of an infiltrating, moderately well-differentiated Vaterian adenocarcinoma (Fig. 4).

Following 1 week of hyperalimentation a successful pancreaticoduodenectomy was performed. Histologic examination of the specimen revealed a 4-cm malignant ampullary adenocarcinoma; two of seven lymph nodes were positive for tumor. The immediate postoperative period was complicated by bilateral lower lobe pneumonia. The patient was discharged 1 month following the procedure. Case 2 was free from disease for approximately 1 year after operation when CAT scan confirmed the presence of hepatic and regional metastases. A moderate objective response was observed with 5-fluorouracil (5-FU) therapy. The patient died 18 months after surgery with extensive recurrent intra-abdominal disease. Postmortem examination was not obtained. Case 2, whose tumor was large and infiltrating with metastatic lymph nodes, exhibited biologic aggressiveness. In comparison the tumor in Case 1 was small without lymph node involvement and was less aggressive.



FIGS. 1A and B. *A.* CAT of Case 1. *B.* ERCP of Patient 1. CBD = common bile duct; PD = pancreatic duct.



FIGS. 2A and B. Photomicrographs of Case 1. PAN = pancreas; AMP = ampulla of Vater. (A): original magnification by 2.5. (B): original magnification by 10.

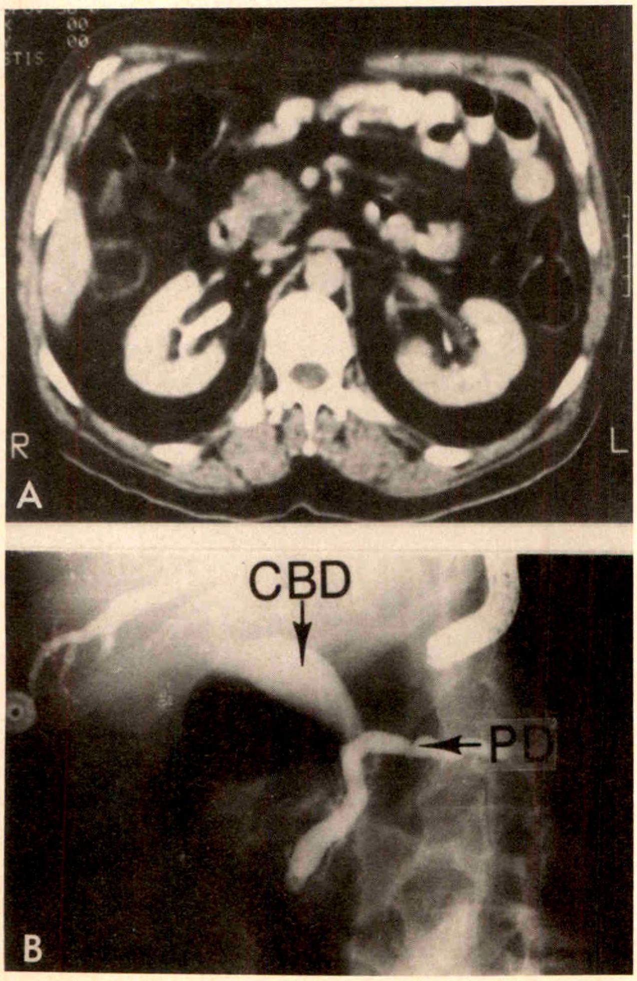
Chromosome analysis of both patients demonstrated no morphologic abnormality in either patient with conventional G-banding, C-banding, and karyotypes. HLA typing failed to reveal any significant correlation between these siblings: HLA typing on Case 1 was A11, A33, B8, DR1, DR7; while Case 2 was A2, A3, B44, D35, DR1, and DR5 (Table 2).

Flow cytometry studies were performed to determine ploidy distribution in deparaffinized tissue specimens. Flow cytometric DNA analysis of cell nuclei stained with propidium iodide revealed two normal DNA distributions including normal percentages of cells in both G0–G1 and G2–M phases. Two other DNA distributions were identified as abnormal: one exhibited a hypodiploid distribution of cells included in the G0–G1 phase and the other exhibited a tetraploid distribution of cells. Peak channels for the cells in the DNA distribution are as follows: the normal DNA distributions were from normal tissue; the abnormal DNA distributions (tetraploidy) represented malignant tissue.

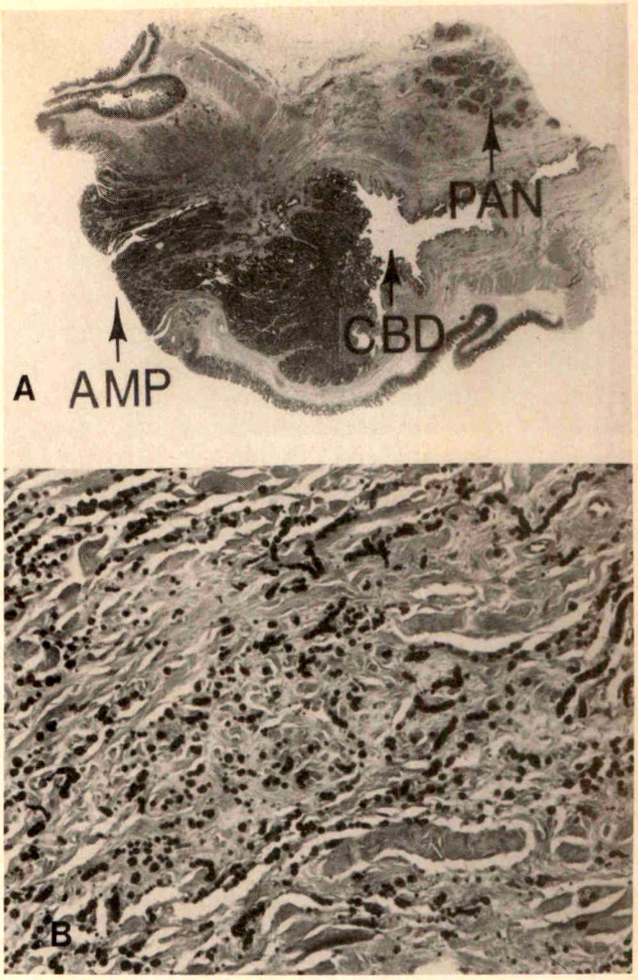
An outline of this kindred presented in Figure 5 reveals a younger sister who had an exploratory laparotomy at another hospital in 1979. The operative findings were compatible with a periampullary neoplasm, although it was not possible to determine the specific site of origin. Intraoperative biopsy of a liver nodule confirmed the presence of metastatic cancer. Investigation of other available siblings revealed evidence of an occasional gastrointestinal polyp but no evidence of FPC.

Discussion

The presence of ampullary carcinoma in two male siblings simultaneously presenting within 2 weeks of each other in their seventh decade, and the identification of a third sibling deceased from a periampullary malignancy, suggests a phenotypic expression of a deleterious gene and not a chance occurrence. The odds against two siblings out of 11 developing pancreatic cancer in the same year, in the absence of a genetic factor, is 100,000,000:1. Cancer of the ampulla of Vater is even more rare, and the odds are even greater against two siblings developing the disease. Previous authors have associated periampullary cancer with FPC and GS.[3–6]



FIGS. 3A and B. *A.* CAT of Case 2. *B.* ERCP of Patient 2. CBD = common bile duct; PD = pancreatic duct.



FIGS. 4A and B. Photomicrographs of Case 2. PAN = pancreas; AMP = ampulla of Vater. (A): original magnification by 2.5. (B): original magnification by 10.

Vaterian cancer, like other malignancies with limited numbers available for study, has not undergone careful epidemiologic review. The influence of genetics on this neoplasm has been given little attention with regard to its pathogenesis. Geneticists understandably have concentrated their studies on unifactorial disorders that occur more frequently in the population. This neoplasm, in the absence of an identifiable single-gene determined etiology, should be considered multifactorial in origin. Such multifactorial disorders are presumed to result largely from the additive effect of a number of factors, some genetic and others environmental.[7] A variety of aneuploid states, single-gene disorders, and other

TABLE 2. *HLA Typing*

Case 1	Case 2
A11 A33 B8 DR1 DR7	A2 A3 B44 D35 DR1 DR5

polygenic conditions may predispose to malignancy, although the exact molecular mechanisms are rarely clear. The complexity and importance of host factors in such tumors become increasingly important and are very difficult to discern.

The most attractive hypothesis for the simultaneous occurrence of this unusual phenomenon is that it is a variant of FPC or GS. It is difficult for the surgeon and pathologist to differentiate between carcinoma arising from the mucosa of the second part of the duodenum, the ampulla of Vater, and the intramural segments of the common bile and pancreatic ducts. Periampullary carcinoma has been described in approximately 30 patients with GS and is recognized as more than a chance occurrence in this syndrome.[2–5] The wide spectrum of extracolonic manifestations identified with GS reflects the variability of gene penetrance. Whether or not a familial occurrence can be implicated in ampullary carcinoma without colonic polypoid disease is conjectural. Neither of these siblings demonstrated colonic or other manifestations of GS as evidenced by normal physical examination, barium enema, and skeletal survey.

The familial aggregation of site-specific neoplasms should be confirmed by pedigree analyses. Of the 11 siblings in this kindred, the two probands and the younger sister discussed in this report died of ampullary or periampullary cancer. Four of the remaining eight have expired of cirrhosis, diphtheria, blood poisoning, and a cerebrovascular accident. Only one of the four living siblings has exhibited interest and agreed to a screening and follow-up studies. One proband worked in a flour mill and the other was a crane operator. No significant environmental or unusual lifestyle circumstances were discoverable from interviews with multiple family members; hence this unique occurrence cannot be accounted for by any known environmental factors.

In the cancer family syndrome a pattern of malignancies emerges, although every individual does not necessarily have the same neoplasm. Familial tumors share several cardinal features: (1) they tend to occur at an earlier age, often 12–15 years before sporadic cases appear; (2) there is an increased incidence of synchronous and metachronous lesions; (3) they may be multicentric and/or bilateral where paired organs exist; (4) there is an excess of 25% of the family members affected who are in direct lineal descent from the proband; and (5) the cancer predisposition in these families behaves as an autosomal dominant trait with a 60% or more penetrance.

There are several possible explanations for the phenotypic expression of Vaterian cancer in these male siblings. The tumors in this family may be due to: (1) chance alone, although this is unlikely; (2) the late penetrance of a GS genotype; (3) tumor heterogeneity caused by a different allele at the same locus; or (4) a pleiotropic manifestation of a cancer-prone genotype being expressed as a result of environmental changes.[6]

In 1935 Cabot[3] described a 36-year-old man (Case No. 21061 from the Massachusetts General Hospital) with weakness, diarrhea, ankle edema, and jaundice

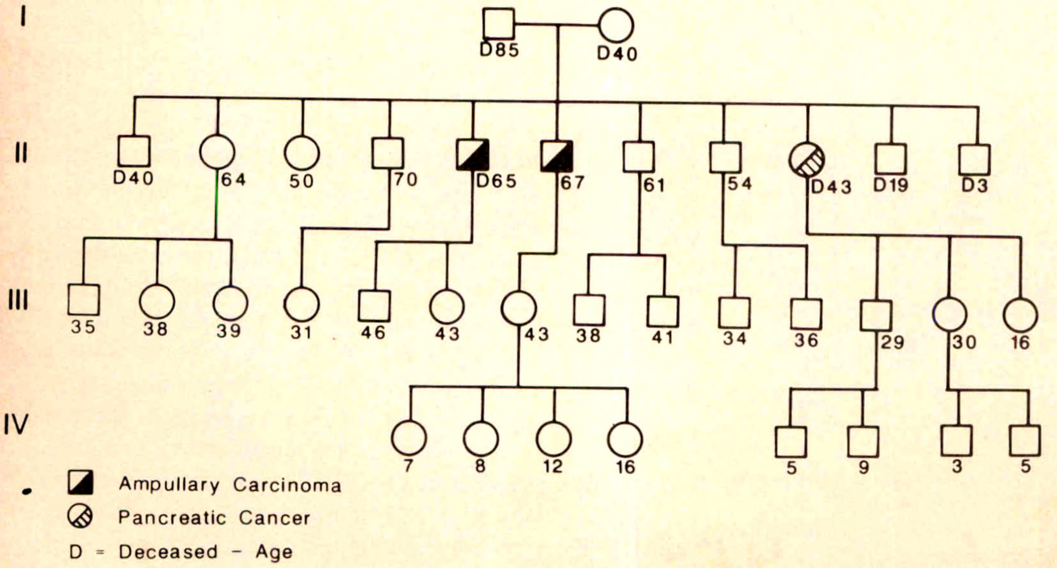


FIG. 5. An outline of kindred for Cases 1 and 2.

who had several manifestations of GS (Table 3). At abdominal exploration for obstructive jaundice he was found to have an ampullary cancer and multiple intestinal polyps. No segment of the gastrointestinal tract greater than 3 cm in length was uninvolved with polyps. Bony exostosis existed in this deformed male with a prior history of having several hard masses removed from the skull, ribs, and mandible. He also had a previously resected fibrosarcoma. His grandmother died of carcinoma (site unknown) and his mother of rectal carcinoma at age 34. Multiple members of the family (mostly females) and their offspring for three previous generations were afflicted with similar bony growths.

Macdonald et al.[4] in 1967 reported two cases associating GS with FPC and periampullary malignancies. Both patients had clinical evidence of FPC and GS. However, one of the periampullary malignancies was located in the head of the pancreas and the other in the ampulla of Vater. One patient had an associated renal adenoma and the other a papillary duodenal adenoma at some distance from the ampulla.

Watne et al.[5] in 1975 reported 11 families with GS involving 280 patients. Two associated cases of Vaterian cancer, one malignancy in the liver and one in the pancreas, were present in these cohorts. However, in 41 cases intestinal cancer developed, often appearing at an earlier age for each successive generation.

Nance and Jones[2] in 1977 reported three females with carcinoma of the ampulla of Vater, all of whom had FPC. Two of their cases were from the same kindred. All of their patients fulfilled the criteria of Morson and Bussey[8] for the diagnosis of FPC; however, none expressed the classic features of GS as they are currently known. They postulated that GS should be viewed as an extracolonic variant of FPC and not as a separate disease process. They also concluded that the FPC patient having extracolonic lesions was an example of GS.

Lynch et al.[6] in 1985 reported a family study of pancreatic carcinoma and hereditary nonpolyposis colorectal cancer. This kindred exhibited vertical transmission of cancer through five generations with a high frequency of associated hereditary nonpolyposis colorectal cancer. They appropriately suggested a need for more biomarker and pedigree studies with better documentation of cancer at all sites.

Several factors mitigate against the diagnosis of GS in the cohort group: no polyps; the absence of extracolonic manifestations of FPC; the absence of metachronous or synchronous lesions; and no instances in this family up to the present time of osteomas, soft tissue tumors, dental anomalies, thyroid cancer, ovarian or carcinoid tumors, lymphoma, fibrosarcoma, brain tumor, skin pigmentation, or FPC.[2,9-11]

In tumors that are heritable, two mutation events are required, the initial one being germinal and the second somatic.[7] Nonfamilial tumors tend to be unifocal and appear at a later age because two distinct somatic events would be required for tumor development. Implicit in this two-hit hypothesis is the assumption that carcinogenesis is related to discrete random changes occurring at a constant average rate. The occurrence of these ampullomas in the seventh decade in male siblings would presently be better placed in the nonfamilial category until such time as there is greater penetrance and expressivity to suggest a diagnosis of GS or FPC.

TABLE 3. *Study Comparison*

Author	Year	Age (yr)/Sex	Site	FPC	GS
Cabot[3]	1935	35/M	AV	Yes	Yes
Macdonald et al.[4]	1967	36/F	PH	Yes	Yes
		44/M	AV	Yes	Yes
			AV	Yes	Yes
			AV	Yes	Yes
Watne et al.[5]	1975		AV	Yes	Yes
Jones and Nance[2]	1977	67/F*	AV	Yes	Yes
		49/F*	AV	Yes	?
		63/F	AV	Yes	?
Lynch et al.[6]	1985	55/M	PH	HPNCC	No
Austin et al. (this study)	1987	64/M†	AV	No	No
		64/M†	AV	No	No

* Same kindred.
† Same kindred.
AV = ampulla of Vater.
PH = pancreatic head.
HNPCC = hereditary nonpolyposis colorectal cancer.

Of the 12 cases reviewed in this communication with the association of Vaterian carcinoma, FPC, and GS,[3-6] three of the tumors were periampullary (25%), not specifically Vaterian in origin (Table 4). Confirmed FPC was reported in nine cases (75%) and in a single case of hereditary nonpolyposis colorectal cancer. Six of the 12 cases (50%) met reasonable criteria for a diagnosis of GS. If the assumptions of Jones and Nance[2] are valid, these numbers would then increase to nine of 12 (75%). No specific trend in morphologic categorization using the criteria outlined by Blumgart and Kennedy[1] could be ascertained. The nine ampullomas, according to this categorization would be as follows: Type I, three; Type II, two; and Type III, four. HLA typing when compared with matched controls demonstrated no difference.

TABLE 4. *Association of FPC, GS, and Vaterian carcinoma in 12 patients*
n = 12

	PH	AV	Yes	No
Site	25%	75%	—	—
FPC	—	—	75%	25%
GS	—	—	50%	50%

PH = pancreatic head.

Genetic counseling and screening for these families is important to reduce their obvious hidden family anxiety. In the absence of a specific biomarker(s), the accuracy of the pedigree analysis becomes increasingly important requiring histologic confirmation of the disease(s) existing in this kindred. Where biochemical markers exist they must be obtained and repeated as part of the follow-up process. Syndromes such as FPC and GS seldom present all of their classic features when initially discovered. The unfolding and phenotypic expressions among these cohorts require close monitoring. The importance of this familial or hereditary pattern of tumor distribution is emphasized by the recent report of their improved survival.[12]

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DISCUSSION

DR. ALVIN L. WATNE (Peoria, Illinois): First, I want to extend my welcome to Claude and Betty on their membership in the Association.

I want to congratulate the authors on what I think is a very important observation. Opportunity comes to those who have an alert mind and make a critical observation, and I want to thank them for sharing their manuscript with me. I took the liberty to bring along a few slides. I've assured Claude that I would not have a 29-page discussion.

(Slide) The question came up about the relation to Gardner's Syndrome. Both Gardner himself and our group now feel that Gardner's Syndrome is probably the ultimate manifestation of the inherited characteristic. As you can see, 60% had soft tissue tumors, 30% had bony tumors, and two-thirds of them showed polyps, so we had patients with soft tissue tumors and no polyps. We had patients with polyps and no soft tissue tumors.

(Slide) Here is this broad group of manifestation of tumors that show up in this syndrome that Dr. Organ referred to, and you will notice that two of our patients had carcinoma of ampulla of Vater.

Dr. Julian Ambrose took a look at this group of patients, and he said, "It looks like you were feeding them a carcinogen." The patients with carcinoma of the ampulla of Vater had no other manifestations of Gardner's Syndrome. However, relatives in their families did show the syndrome.

(Slide) One of these patients was particularly interesting. This 18-year-old girl entered our hospital in 1973 with (by history and physical examination) an obvious carcinoma of the ampulla of Vater.

Her colon had been removed for polyps 2 years previously. She underwent a decompression cholecystojejunostomy, and, at that time, we could palpate a small tumor at the ligament of Treitz. After about an 8-week period, she then underwent a pancreaticoduodenectomy, including the gallbladder and the cholecystojejunostomy, and during that interval of about two months, she had developed another adenomatous polyp right at the cholecystojejunostomy.

(Slide) In 1978, this girl developed a cyst-adenocarcinoma of the ovary, and in 1982, we removed her rectal segment for three carcinomas that had developed despite repeated proctoscopic examination; so this girl manifested three different malignant neoplasms in her life.

(Slide) That brought us to study any associated inherited characteristics, and in our patients we found that there was a marked increase in the cholesterol fraction and the primary bile acid fraction in the fetal steroids of patients with polyposis coli or Gardner's syndrome.

We have also recently seen that there is an increase in the glycosyl transferase activity and a decrease in the glycoprotein formed in the colonic mucosal cell wall of these patients.

(Slide) One last point that will lead to a question: These patients have been shown by Utsunomiya to develop gastric and duodenal polyps. So I will now ask some questions of Dr. Organ, if I might.

The first question would be: Have you noticed any other physiological or biochemical changes such as alterations in fecal steroids, bile salts and increased or decreased incidence of cholelithiasis.

Have you extended your study of your patients to the cousins? You must extend that family group that you showed us because the manifestations may appear in other family members. The patients may have expired before the manifestations appeared, and the trait will show up in the next generation. Have you any data regarding the incidence of polyps of the upper gastrointestinal tract in these patients, and what would be your approach to an adenomatous polyp of the upper gastrointestinal tract in these patients?

DR. F. CARTER NANCE (Livingston, New Jersey): I enjoyed Dr. Organ's and Dr. Watne's paper and would like to give one of my own.

(Slide) Dr. Organ was kind enough to mention my study. We found a similar problem and reviewed 19 reported cases of periampullary carcinoma in patients with Gardner's Syndrome. We did stretch the diagnosis of Gardner's Syndrome, feeling that any manifestation of the familial polyposis syndrome associated with extracolonic findings should be grouped in that category.

I think the striking thing for us was that most of these patients were presented at an early age with the periampullary carcinoma.

(Slide) And another striking aspect was that the type of periampullary malignancy was ampulla of Vater in most of them—although duodenal pancreatic and undetermined.

As Dr. Watne mentioned, (Slide) our recommendations on the basis of our findings, at least, for the patients who have the marker of familial polyposis are that there be routine surveillance not only of the lower gastrointestinal tract (if any colon is left), but routine surveillance of the upper gastrointestinal tract, endoscopic biopsy removal of all duodenal and gastric polyps and surgical removal of recurrent or malignant polyps.

Unfortunately, in this group of patients that Dr. Organ has presented, there isn't a convenient marker of familial polyposis, and I guess that really raises my biggest question. Has he identified anything in these families that will allow us to identify the cohort and to do some sort of reasonable surveillance in this group of patients?

It is a beautifully studied family, but I would hope that he can extend his familial study, as Dr. Watne suggested, to identify any further members of the cohort and to identify any markers that we could use for rationale surveillance.

DR. JOHN C. MCDONALD (Shreveport, Louisiana): I was honored that Dr. Organ would ask me to discuss his first presentation as a member of this society.

This paper should be considered in the context of a series of publications by Dr. Organ on familial cancer, a subject in which he has had an abiding interest.

In the apparent effort to find some genetic marker to relate to these patients, he studied the HLA locus and found no relationship, and it is that point that I would like to discuss.

Some 20 years ago a small paper was published which seemed to show a relationship between the H2 phenotype and murine leukemia. Shortly thereafter, immune response genes were discovered and related to the major histocompatibility locus. These two observations set in motion an avalanche of studies all designed to relate some disease state to the HLA phenotype or genotype.

Some 20 years later there are at least four or five dozen such conditions well established statistically. These disease processes generally fall into two general categories. One is a series of arthropathies of which Reiter's Syndrome is a prototype, and the other is a large variety of diseases that seem to be related to autoimmunity.

It is ironic that even though the original observation was related to a malignant condition, after 20 years there is not a single human malignancy that appears to have been reliably related to the HLA locus. So while one intuitively believes that there must be a genetic marker or genetic information that is related to these familial cancer syndromes, it appears not to be HLA locus.

DR. CLAUDE H. ORGAN, JR. (Closing discussion): I wish to thank Dr. Watne and Dr. McDonald for their contribution; we relied on their work to point us in the right direction. Research giveth and research taketh away. We have been the beneficiaries since World War II of superb research in the United States and worldwide; and just as research takes procedures away from us, it affords us new opportunities. Genetics offers that opportunity for us.

It is said that the clinician or the clinical investigator is a vanishing breed, and that the basic scientists are in one part of the university and the clinicians in another. It behooves us as clinicians to become involved with these studies. I am not a geneticist, but I realize the benefits that can accrue from this. These pedigree analyses are very difficult to formulate. Again I thank Dr. Austin, one of our very talented residents who has narrowed his interest and talents down to thoracic surgery for dealing with a very difficult family that is fearful of being called a cancer family. Usually there is a family historian to be dealt with whose confidence must be gained, who has a family bible or can give you much of this information.

Dr. Watne, in the large series from Omaha that is masterminded by Dr. Henry Lynch, (glycoproteins or fecal steroids were not dealt with. At the Familial Institute they have had as one of their main areas of concentration the development of pedigree analysis. These are very hard to compile because once you get beyond first-degree relatives in our mobile society, it is difficult to obtain information from second-degree relatives.

These pedigrees have been studied with a number of enzymes and biochemical markers, recently including alpha-fucosidase.

The studies on twins with cancer have been remarkably unproductive. This genotype will be carried by a male and be phenotypically expressed in the next generation in the other sex.

This is a difficult family. We have had a difficult time getting them in, and we don't know what the G. I. tract of many of them really looks like. If polyps are high in the G. I. tract, they should be scoped often and as many of them excised endoscopically as possible. There tends to be an aboral increase in the incidence of malignancy or the propensity toward malignancy, that is, it would be lower in the stomach than in the colon. Therefore, endoscopic removal of these and endoscopic review of these on a periodic basis, alternating with barium swallow and/or enema, would be indicated.

It has certainly raised the possibility of gastric mucosectomy, a procedure that would be a little more vascular than rectal mucosectomy if you are operating on the same type of stomachs that I am.

Polyamine Levels and Gastrin Receptors in Colon Cancers

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Polyamines and gastrin receptors (GR) were studied in samples of colon cancer and mucosa from 40 patients and in control mucosa from 11 patients without cancer. Polyamines (*i.e.*, putrescine, spermidine, spermine) are essential for growth and differentiation. The concentration of polyamines is elevated in rapidly proliferating normal tissues and in some cancers. The presence of GR in human colon cancers has been previously reported. The purpose of the present study was twofold: (1) to determine whether polyamine levels are elevated in colon cancers and in adjacent normal colon mucosa compared to colon mucosa from patients without cancer; and (2) to examine the relationship between polyamine levels and GR in colon cancers. Polyamine levels in colon cancers were significantly higher than in the normal colon mucosa from the same patients. The polyamines, spermidine and spermine, were significantly higher in colon mucosa from patients with cancer compared to patients without cancer. Spermidine and the spermidine:spermine ratio, an index of cell proliferation, were increased in colon cancers with GR compared to cancers without GR. There were no significant correlations between polyamine levels and the following: patient age, CEA level, site of cancer, stage, or differentiation. Because polyamine levels are increased in colon mucosa from patients with cancer, measurement of polyamines may detect patients at risk for subsequent development of colon cancer. Increased levels of polyamines in colon cancers with GR is evidence that gastrin may play a trophic role in human colon cancers.

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THE POLYAMINES, putrescine, spermidine, and spermine, are small polycations that are essential for the growth of both normal and neoplastic cells.[1] Increased cellular levels of ornithine decarboxylase, the rate-limiting enzyme of polyamine biosynthesis, as well as increased levels of polyamines, occur during cellular differentiation and growth.[1,2] Concentrations of polyamines are elevated in some cancer cells compared to normal cells.[1,2] Polyamines have been linked to the regulation of synthesis of DNA, RNA, and protein[2]; the mechanisms by which polyamines exert these effects are not well understood.

Stimulation of polyamine biosynthesis occurs in the intestine in response to a variety of substances and physiologic conditions. Gastrin stimulates the growth of portions of the normal gastrointestinal tract in many species, including rats[3] and mice.[4] α-Difluoromethylornithine (DFMO), an irreversible inhibitor of ornithine decarboxylase, blocks the trophic effects of gastrin on intestinal growth.[5]

Studies in rats[6] and mice[7] have demonstrated a role of increased polyamine biosynthesis in the development of colon cancers during chemical carcinogenesis. Growth regulation of colorectal cancers that contain high levels of putrescine, spermidine, or spermine may be polyamine-dependent. Such cancers might be successfully treated with polyamine biosynthesis inhibitors. It has been previously reported that DFMO inhibited growth of the MC-26 mouse colon cancer *in vivo* and *in vitro*,[8] and inhibited growth of two human colon cancers growing in nude mice.[9]

The relationship between gastrointestinal hormones and their receptors in malignant cells has been recently

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reviewed.[10] It has been previously reported that normal human gastric and colonic mucosa and adenocarcinomas of the human stomach and colon contain specific gastrin receptors (GR).[11] The functional significance of GR on these human cancers is not yet clear.

Winsett et al.[4] found that treatment with pentagastrin, an analog of gastrin, enhanced growth of MC-26 mouse colon carcinoma and decreased the survival of treated mice; MC-26 colon cancer cells have specific, high-affinity GR. Beauchamp et al.[12] reported that proglumide, a GR antagonist, inhibited MC-26 colon cancer growth and prolonged survival in tumor-bearing mice. Chronic endogenous hypergastrinemia induced by antral exclusion in rats was reported by McGregor et al.[13] to significantly increase the growth of carcinogen-induced colon cancers. Growth of human colon cancers growing in nude mice[14] and in tissue culture[15] has been stimulated by gastrin.

The purpose of this study was to determine whether concentrations of polyamines are elevated in colon cancers and in adjacent normal colon mucosa in cancer patients compared to colon mucosa from patients without cancer, and to examine the relationship of polyamine levels in colon cancers to the GR content of cancers. The relationships between polyamine levels and age of patient, preoperative CEA level, site of colon carcinoma, histologic differentiation, and clinical stage of disease were also examined.

Materials and Methods

Specimens of primary colon cancers were obtained at the time of surgical resection from 40 patients treated at the authors' institution. The age of the patient and preoperative CEA level, as well as site of colon cancer, were recorded. The colon was divided into left and right sides, according to embryonic development; the right side (midgut) included the cecum, ascending colon, and transverse colon; the left colon (hindgut) included the splenic flexure, descending colon, sigmoid, and rectum.

All specimens were examined by a surgical pathology service. Immediately upon removal of the surgical specimens, portions of viable cancer and normal colon mucosa were excised for measurement of polyamine levels and GR. Frozen sections of the cancer adjacent to the excised portion were examined for confirmation of viable cancer. Normal mucosa was obtained from the margin of the resected colon; the absence of cancer at the margins was confirmed histologically. Specimens were snap-frozen in liquid nitrogen and stored until analysis.

The histologic diagnosis of colon carcinoma, the degree of differentiation, and the Astler–Coller modification of Dukes' classification of stage of disease[16] were determined by a surgical pathologist who had no knowledge of the results of GR analysis. Mucoid adenocarcinomas were classified separately because these tumors have a particularly poor prognosis even if the tumor is well differentiated and no lymph node metastases are present.[17]

Colon mucosa was obtained from 11 patients who had colon resection for non-neoplastic disease. Ten patients had colon resection for diverticulosis and one patient for a benign stricture. Specimens were examined histologically by a surgical pathologist to assure specimens were uninvolved with any inflammatory process or occult malignancy.

Polyamine Analysis

Tissue was homogenized in 4% sulfosalicylic acid (2 mL/g tissue), then incubated on ice for 30 minutes. The homogenate was then centrifuged at 10,000 g for 10 minutes. Aliquots of the supernatant remaining after centrifugation were analyzed using a Dionex 2110i high pressure ion chromatography unit (Dionex Corporation, Sunnyvale, CA). Polyamines were eluted using orthophthaldehyde at a flow rate of 36 mL/h. Putrescine was eluted with 0.167 mol/L K^+ buffer (pH 5.65). Spermidine and spermine were eluted with 0.66 mol/L K^+ buffer (pH 5.65). Polyamine concentrations were expressed as nmol/mg of protein. Protein content was determined by the method of Lowry et al.[18]

GR Analysis

The content of GR of the colon cancer and normal mucosal specimens were determined by methods previously described.[11] Briefly, specimens were excised and washed in ice-cold buffer A (TRIS 10 mmol/L; NaCl 137 mmol/L; KCl 5 mmol/L; CaCl 2 mmol/L; MgCl 2.5 mmol/L; and sucrose 0.25 mmol/L at a pH of 7.4), containing 0.1% bovine serum albumin (BSA, fraction V from Sigma) and then snap-frozen in liquid nitrogen and stored at −70 C. Frozen tissues were weighed and pulverized with a thermovac autopulverizer cooled in liquid nitrogen. The resulting powder was homogenized in 5 volumes of buffer A plus BSA, using a precooled polytron homogenizer (PG-10ST, Brinkman Industries, Westbury, NY). The homogenate was filtered through a double layer of cheese cloth, presoaked in ice-cold buffer A, and subjected to 200 g for 10 minutes of centrifugation to remove any cell debris. For the preparation of total crude membrane fractions, the resulting supernatant was subjected to 30,000 g for 45 minutes centrifugation in a fixed angle SM-24 rotor. The resulting pellets were then washed once again with buffer A plus BSA and repelleted at 30,000 g for 45 minutes. The pellet

TABLE 1. *Polyamine Levels (nmol/mg protein) in Left- and Right-sided Colon Cancers*

	Left (N = 25)	Right (N= 15)
Putrescine	1.33 ± 0.48	1.00 ± 0.08
Spermidine	4.50 ± 0.49	4.46 ± 0.74
Spermine	5.84 ± 0.47	5.67 ± 0.55
Spermidine:spermine ratio	0.76 ± 0.04	0.81 ± 0.08

obtained was resuspended in a buffer B (HEPES 25 mmol/L; MgCl 2.5 mmol/L; KCl 5 mmol/L; NaCl 137 mmol/L; $NHPO_4$ 0.7 mmol/L; glucose 10 mmol/L, pH 7.4) plus BSA, homogenized manually with a glass teflon homogenizer and processed for measurement of protein[18] and GR.

Synthetic human gastrin-17-I (Bachem, Torrance, CA) was iodinated as previously described.[11] The biologic activity of iodinated gastrin molecules is similar to that of an equimolar concentration of noniodinated gastrin. Aliquots of the membrane suspension in buffer B plus BSA, containing approximately 200 μg of protein, were used as substrate in each tube. A multipoint saturation analysis (7–10 points per assay), using increasing concentrations of radiolabeled gastrin (0.01–0.05 mmol/L) with (nonspecific binding) or without (total binding) 1000-fold excess of radioinert gastrin was carried out, and the binding was analyzed by a Scatchard plot of the specific binding data. The binding assay was performed at 30 C in a water bath for 30 minutes, after which the tubes were chilled on ice and 100 μL of ice-cold buffer B plus BSA added. The peptide hormone bound to the substrate was separated from the excess unbound hormone by filtration over cellulose acetate filters using a multifiltration unit (1225 sampling manifold, Millipore). The membrane filters containing the substrate were placed in a glass tube and counted in a gamma counter (Beckman Model 5550, with 78% efficiency for iodine 125 counting).

Data Analysis

The relationship between the age of the patient or the preoperative CEA levels compared to the polyamine concentrations of colon cancers and of normal mucosa from patients with colon cancer were each examined by means of linear regression analysis. The mean putrescine, spermidine, and spermine concentrations were determined in groups of patients with cancers of different degrees of histologic differentiation and stage of disease (Stages A and B *vs.* Stages C and D). Differences between groups were analyzed by the Kruskal–Wallis test and the Mann–Whitney test. A value of $p < 0.05$ was considered significant. Polyamine levels in normal colon mucosa of cancer patients were compared to the levels in colon cancers, as well as to colon mucosa from patients without cancer, by the Kruskal–Wallis test and the Mann–Whitney test. Polyamine concentrations in cancers with high-affinity GR were compared to concentrations in cancers without GR.

The spermidine:spermine ratio[19] (an index of cell proliferation that is increased in rapidly proliferating tissues) was also compared in the different groups.

Results

Of the 40 patients with colon cancer in the study, 25 had cancers arising from the left side of the colon and 15 had cancers arising from the right side. There were no significant differences in polyamine levels between left- or right-sided cancers (Table 1). Polyamine levels of colon cancers or normal mucosa from patients with colon cancer did not correlate with patient age or with preoperative CEA level (data not shown).

Putrescine, spermidine, and the spermidine:spermine ratio were significantly increased in colon cancers compared to the colon mucosa from the same patients (Fig. 1). Spermine levels were not significantly different between colon cancers and normal colon mucosa from the cancer patients. Levels of spermidine and spermine were also increased in the normal colon mucosa from cancer patients compared to the normal colon mucosa from patients without cancer (Fig. 1).

Spermidine and spermine were both significantly elevated in the colon mucosa from cancer patients compared to the colon mucosa from patients without cancer. Spermidine was 1.78 ± 0.21 nmol/mg protein in control colon mucosa and 3.50 ± 0.37 nmol/mg protein in colon mucosa from cancer patients. Spermine was 3.50 ± 0.48 nmol/mg protein in control colon mucosa and 5.32 ± 0.32 nmol/mg protein in colon mucosa from cancer patients. The spermidine:spermine ratio of normal colon mucosa from cancer patients was increased compared to normal colon mucosa from patients without cancer (Fig. 1).

The relationship of polyamine levels in colon cancers and normal colon mucosa from cancer patients was examined by linear regression analysis (Figs. 2 and 3), and a significant correlation was found between the levels of putrescine (Fig. 2) and spermidine (Fig. 3) in both cancers and mucosa.

In reviewing the Dukes' classification of the colon cancers, two patients had a Stage A cancer, 13 were Stage B, 18 were Stage C, and seven were Stage D. The mean levels of polyamines and the spermidine:spermine ratio were not significantly different in cancers from patients with early stages of disease (A and B) compared to cancers from patients with more advanced disease (C and D) (Fig. 4).

Seven of the colon cancers were well differentiated, 23 were moderately or poorly differentiated, and four were

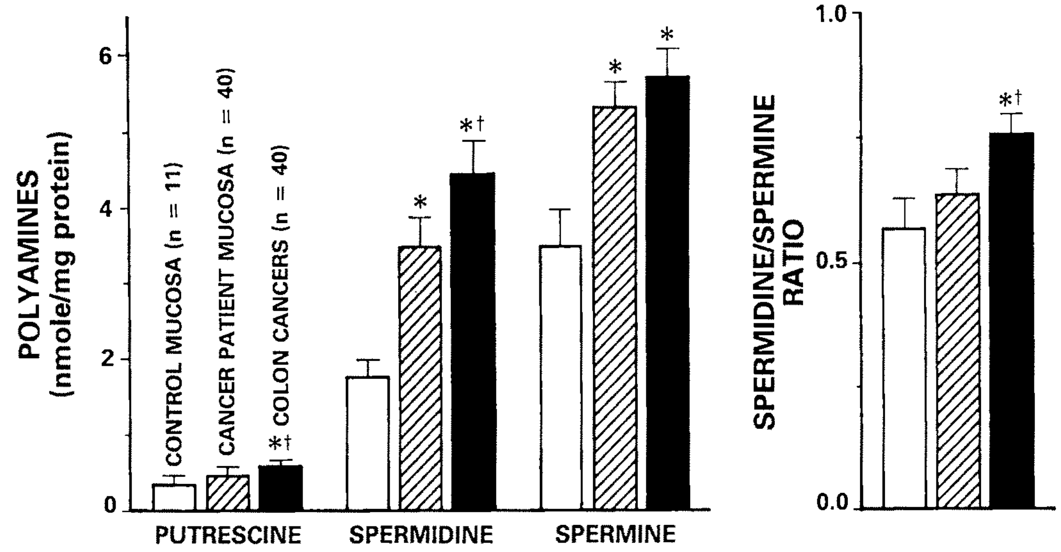

FIG. 1. Polyamine concentrations in control colon mucosa, cancer patient colon mucosa, and colon cancers. $*p < 0.05$ compared to control; $\dagger p < 0.05$ compared to cancer patient colon mucosa.

colloid adenocarcinomas. There were no significant differences in cancer polyamine levels among cancers of different degrees of histologic differentiation (Fig. 5).

GR analysis was done on 30 of the colon cancer specimens. Fifteen (50%) had cancers with no detectable specific high-affinity ($K_d < 1.0$ nmol/L) GR, and 15 cancers tested had specific high-affinity GR levels that ranged from 1.5 to 50 fmol/mg protein. Spermidine levels were significantly increased in GR-positive cancers compared to GR-negative cancers (Table 2). Putrescine and spermine levels were higher in the cancers with high-affinity GR, although the differences were not significant. The spermidine:spermine ratio was significantly higher in cancers with high-affinity GR compared to cancers that had no GR.

Discussion

Elevated levels of polyamines in colon cancers compared to normal colon mucosa from the same patients have been demonstrated. In addition, polyamine levels

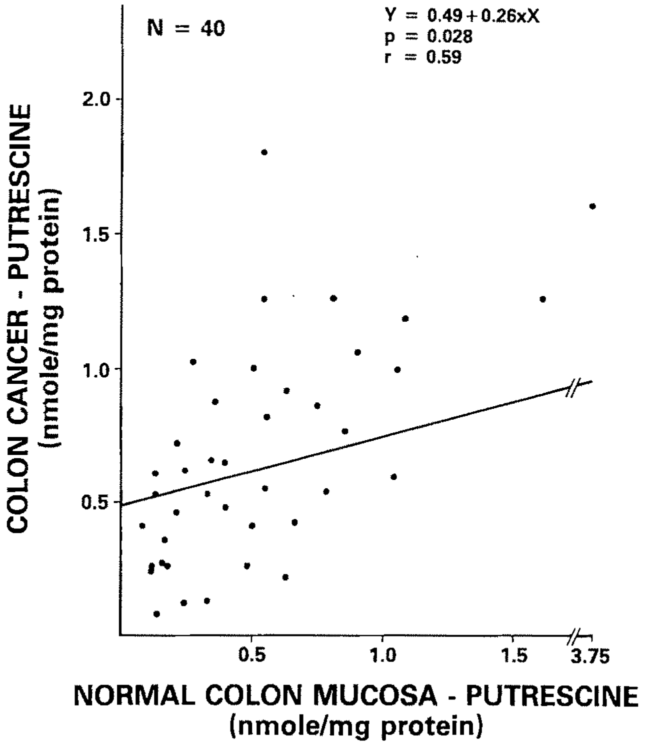

FIG. 2. Linear regression analysis of putrescine concentrations in colon cancers and in normal mucosa from the same patient.

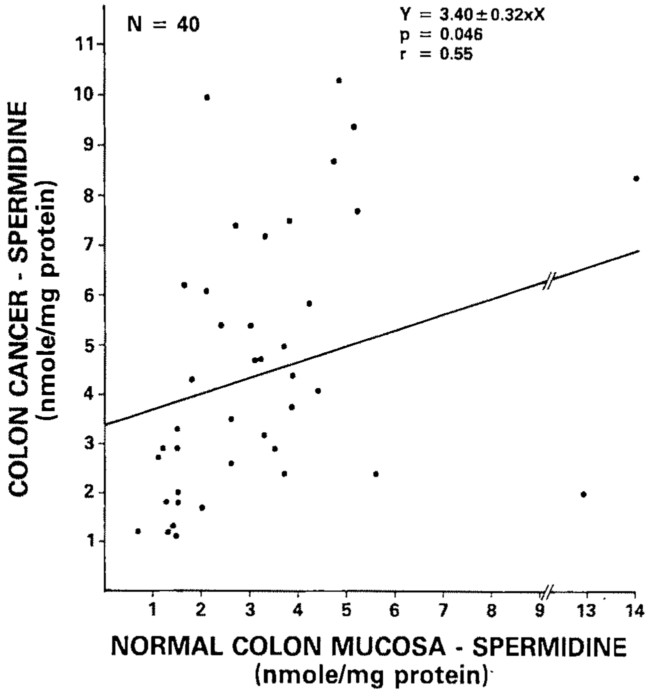

FIG. 3. Linear regression analysis of spermidine concentrations in colon cancers and in normal mucosa from the same patient.

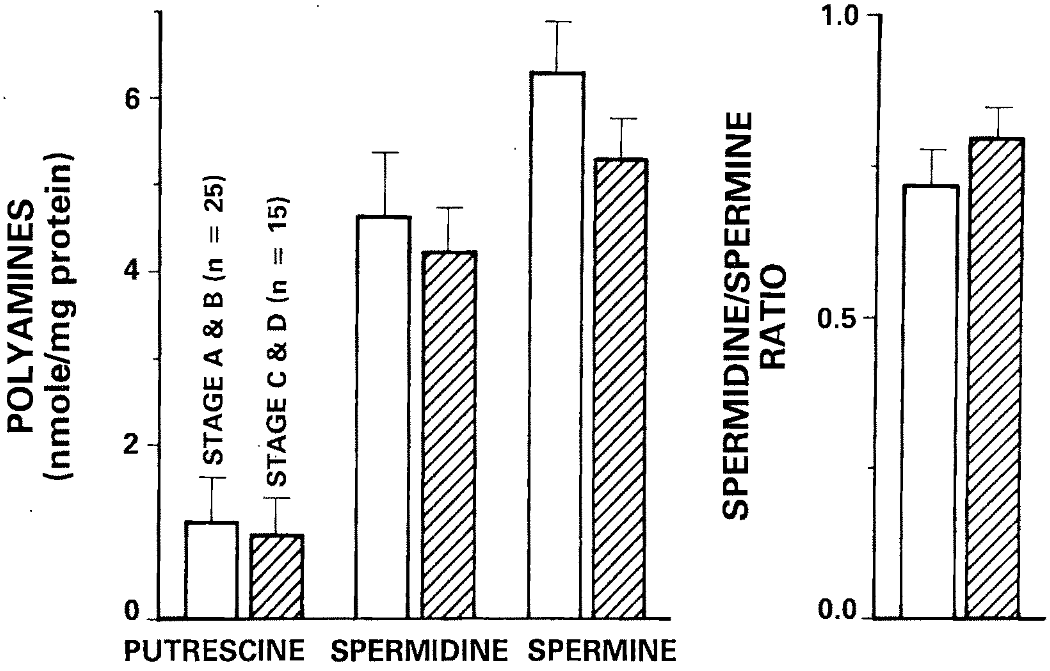

FIG. 4. Tumor polyamine concentrations and stage of colon cancers.

in the normal colon mucosa from cancer patients were significantly higher than levels in normal colon mucosa from patients who underwent colon resection for nonneoplastic disease. These findings suggest a generalized abnormality in the colon mucosa of patients with colon cancer. These findings agree with those of LaMuraglia et al.[20] who reported increased ornithine decarboxylase (ODC) activity and polyamine content in noninvolved colon mucosa from patients with colon cancer compared to colon mucosa from patients without neoplastic disease.

The elevated levels of polyamine in colon cancers in comparison to those of normal colon mucosa have been previously reported.[20-23] Kingsnorth et al.[22] found that spermidine levels were threefold greater and spermine levels fourfold greater in colon cancers compared to the levels in apparently uninvolved resection margins. Porter et al.[23] analyzed ODC and S-adenosylmethionine decarboxylase (AdoMet DC) activity in various types of colonic neoplasms and found a positive correlation with neoplastic progression of colonic mucosal lesions.

No relationship was found between polyamine levels with age, preoperative CEA levels, histologic differentiation, and stage of disease; these findings agree with the studies of Kingsnorth et al.[22] Porter et al.[23] reported increased ODC activity (fivefold to eightfold) in colon cancers compared to normal mucosa, but they found no correlation with the histologic differentiation.

Luk and Baylin[24] found elevated ODC activity in both colonic polyps and in normal-appearing mucosa from 11 of 13 patients with familial polyposis as well as in normal mucosa of first-degree relatives of patients with

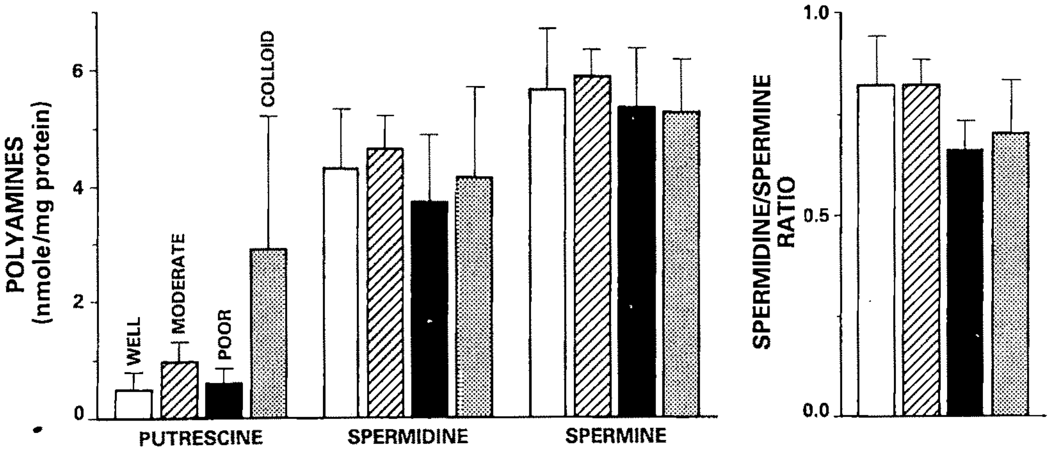

FIG. 5. Tumor polyamine concentrations and histologic differentiation of colon cancers.

familial polyposis. These findings suggest that ODC may be useful in identifying clinically normal family members who carry the polyposis genotype. Increased proliferation of the apparently normal colon mucosa in cancer patients, indicated by increased polyamine biosynthesis, may explain the potential for synchronous and metachronous colon cancers.[25] Increased polyamine levels in apparently normal colon mucosa may be helpful in identifying patients at increased risk of developing colon cancer.

Gastrin stimulates the growth of established colon cancers in mice[4] and enhances colonic and gastric carcinogenesis in rats.[13,26–29] Endogenous hypergastrinemia produced by either antral exclusion or small bowel resection in rats caused increased DNA synthesis in colon tumors or an increased incidence of tumors of the bowel, respectively, in carcinogen-treated rats.[13] Tahara and Haizuka[26] reported that gastrin increased the incidence of carcinogen-induced gastric cancer in rats. Others have found that elevated gastrin levels inhibit the incidence of carcinogen-induced stomach cancers in rats.[27] Singh et al.[28,29] have found that the trophic effects of gastrin on MC-26 mouse colon cancers are mediated by the interaction of gastrin with its receptor.

It has recently been reported that chronic treatment with 3% DFMO inhibits growth of two human colon cancers growing as xenografts in nude mice.[9] The magnitude of tumor growth reduction was greater in the tumor with lower pretreatment polyamine levels. Measurement of polyamine levels in primary colon cancers may have a role in selecting therapeutic agents and in predicting response to treatment.

The significance of these findings is that cell proliferation in normal gastric and colonic mucosa may be controlled, in part, by gastrin and that the growth of colon cancers may also be affected by gastrin. The mechanism of gastrin-stimulated mucosal growth involves polyamine biosynthesis. Polyamines are increased in human colon cancers with GR. The increased levels of spermidine and the increased spermidine:spermine ratio in GR-positive cancers suggest that gastrin may play a role in the cellular proliferation of these cancers compared to GR-negative tumors.

Surgical excision remains the only effective treatment for colorectal cancers. An effective treatment for advanced colon carcinoma has not been developed. Understanding the role of polyamine biosynthesis and its regulation by gastrin in human colon cancers may lead to the development of new treatment strategies that can be used as an adjunct to surgical resection. Antigastrin compounds and inhibitors of polyamine biosynthesis may be promising methods for treatment of selected patients with colonic cancer.

TABLE 2. *Polyamine Levels (nmol/mg protein) in GR-positive and GR-negative Cancers*

	Gr-negative	GR-positive
Putrescine	0.55 ± 0.10	1.65 ± 0.78
Spermidine	3.94 ± 0.70	5.93 ± 0.57*
Spermine	5.18 ± 0.57	6.68 ± 0.63
Spermidine:spermine ratio	0.77 ± 0.08	0.90 ± 0.05*

* $p < 0.05$ *vs.* GR-negative cancers.

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DISCUSSION

DR. JOSEF E. FISCHER (Cincinnati, Ohio): Dr. Townsend has done his usual elegant presentation of an idea that I personally find very exciting.

This is such a good idea—the concept that the gut, which is the most powerful endocrine producing organ in the body, has some effect on the tumors within it—that I personally am very surprised that, with the exception of a few laboratories scattered around the country, one of which is my own department collaborating with Dr. Townsend on pancreatic cancer, this idea hasn't caught on.

The concept is very attractive, and it raises the question of the possibility that, in tumors that heretofore have not been considered under hormonal control, there may, in fact, be a receptor-positive type of tumor that may lend itself to a whole series of other therapies that were mentioned in the manuscript.

I have a few questions for Dr. Townsend and Dr. Thompson.

First, if I understand the way the study was done, the receptor assays and the polyamine assays were done in adjacent mucosa at the margin of resection.

Have you studied the polyamine content of mucosa remote from the cancer area. If you have, have you found the same changes? I realize that is difficult to do, but the difference would be that if the polyamines were elevated in the mucosa from the cancer and not in the resection margin, this would imply an entirely different mechanism than if it were adjacent to the cancer or at the limit of resection, where you may be dealing with a field defect.

I am not very familiar with where these gastrin receptors are, but my second question is: Where are they on the mucosal cell? Are they on the luminal or the abluminal side? If they are on the luminal side, I think this has one implication. My own guess, knowing nothing about the area, would be that perhaps they would be on the abluminal side and perhaps would be a paracrine receptor for gastrin originating in the submucosal ganglia, although I am not certain. I wonder whether you have that information.

A third question concerns the possible mechanism. Do you envision the gastrin interaction with the colonic mucosa and neoplasms to be a mechanism by which changes in diet perhaps influence the development of colonic cancer, since colonic cancer has been related to both meat and fat intake? Perhaps one could make a connection with an intake of meat as releasing gastrin from the oral end of the gastrointestinal tract, but here, again, I am not certain, and I wonder whether your concept of how this evolves involves an environmental or perhaps a genetic component.

The fourth question is actually one of mechanism. Despite the fact that ornithine decarboxylase is supposed to be the rate limiting enzyme in this cascade of polyamine synthesis, I was intrigued by the manuscript's presentation of what seemed to be different ratios between these three polyamines. For example (not shown on the slides, but in the manuscript), the colloid variety of carcinoma had a very high concentration of putrescine as compared to spermine and spermidine, and although you have made an analysis of the spermidine to spermine ratio, do you have any thoughts about what the relationship between these three polyamines may, in fact, mean?

I enjoyed the manuscript and the presentation very much and I thank you for the privilege of discussing it.

DR. EDWARD M. COPELAND III (Gainesville, Florida): I want to congratulate Courtney Townsend and Jim Thompson on the evolution of their work on hormone receptors, and particularly their work on gastrin receptors in various gastrointestinal tract tumors.

Dr. Townsend has pointed out to us today that polyamine levels are elevated in rapidly growing tissues.

An associate of mine while I was at the M. D. Anderson Hospital, Dr. David Ota, has recently discovered that polyamine concentration in red blood cells is elevated in a rat-tumor model in which malnourished rats are replenished with total parenteral nutrition (TPN). Red blood cells have an affinity for circulating polyamines, and red cell content can be reflective of polyamine synthesis. Dr. Ota interprets his data to indicate that TPN has stimulated tumor growth in his rat model.

My interpretation of this and other rodent studies is that TPN is stimulating growth of noncancerous tissues as well, and therefore an increase in polyamine levels cannot be interpreted solely as an indicator of tumor growth. Thus, I am not certain of what predictive value polyamine levels will be, since both normal and abnormal tissues in replication emit them.

Gastrin, on the other hand, does have a trophic role for many of the normal gastrointestinal tissues. When I was in Houston, our group showed gastrin to be trophic for the small bowel, pancreas, and colon. I am intrigued by Dr. Townsend's discovery of gastrin receptors on colon carcinoma cells and by the possibility that these receptors are responsible for the trophic behavior of gastrin on gastrointestinal tumors.

I am curious to know if colon cancer is more prevalent in patients who have elevated serum gastrin levels. What are the polyamine levels in normal colonic mucosa of patients who have elevated serum gastrin levels? Certainly your group at the University of Texas Medical Branch in Galveston has the patient population to answer such questions for us.

Again, Dr. Townsend, my congratulations on a very fine manuscript.

DR. GEORGE L. IRVIN III (Miami, Florida): I would just like to re-emphasize one of the questions that Dr. Fischer asked.

It is very important to look at the field change in these colon cancer patients. I would just like to ask the authors if there is a field change with your polyamines or with your gastrin receptors close to the tumor which may influence lines of resection and recurrence rates?

My other question is: Have you looked at other benign or premalignant polyps in the colon?

DR. COURTNEY M. TOWNSEND, JR. (Closing discussion): I would like to thank the discussants for their comments.

Dr. Fischer and Dr. Irvin, the polyamines and the gastrin receptors in the mucosa of colon cancer patients were obtained from the margin of the resection. It was usually from the proximal margin, and that was the longest margin. We don't know anything about possible field changes. That is very interesting, and I think very important potentially, and we will certainly begin to take multiple samples at different distances from the tumor.

As far as testing any other part of the colon that is left in place, we have not done that.

The gastrin receptors are membrane receptors.

Whether dietary changes associated with colon cancer work through gastrin mechanism, again I am not sure, although protein is one of the strongest stimulants for gastrin release.

The relationship of putrescine to the other polyamines spermidine and spermine is inconstant. It is the shortest half life of polyamines, and the only ratio that has been found to be constant, at least in normal tissues, in the few cancers that we have studied, has been the spermidine-spermine ratio.

Dr. Copeland, obviously we followed the lead of your group in evaluating the effects of gastrin on tumors arising from the mucosa of the colon. The predictive levels of polyamines in serum and other body fluids that Ota and his colleagues have used may not be so useful in determining the extent of tumor, the rapidity of growth, or even the selection of patients for treatment with polyamine inhibitors, simply because the red cell does act as a sink. However, determination of polyamine levels in the tumors may be very important. We have found in tumors growing in athymic nude mice (four different human colon cancers, two different stomach cancers, and three pancreatic cancers) that sensitivity of the tumors to inhibition by DFMO is inversely related to level of polyamines. We might think that the higher the level of polyamines, the greater the requirement for the tumor growth. As a matter of fact, the more they have, the easier they can avert the adverse effects of inhibition.

The question about serum gastrin levels and development of subsequent cancers is one that we are not able to answer at this time. Travis Solomon and his colleagues in Columbia, Missouri published an abstract a year and a half ago that showed that fasting serum gastrin levels were elevated in about 20% of colon cancer patients. At the present time, we have an ongoing study to evaluate serum gastrin levels, both fasting and food-stimulated, in colon cancer patients.

We have established a human gastrinoma in nude mice that we have had successfully transplanted now for three years. It produces functionally active gastrin in that the stomachs grow large but the colon mucosa, for some reason, does not become hyperplastic in the nude mice. So what the relationship is there, I can't answer.

Is Total Pelvic Exenteration Reasonable Primary Treatment for Rectal Carcinoma?

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Total pelvic exeneration (TPE) is reasonable primary surgical therapy in select patients with large bulky locally invasive rectal cancers that can be removed *en bloc.* Many do not have either nodal or distant metastasis. Furthermore, TPE can be curative and often is palliative for similar lesions that are recurrent or nonresponsive to radiation therapy. Operative mortality rates should be under 10% and can be under 5% for primary cases. Although improvement in preoperative management and operative technique, especially with urinary conduits and postoperative care is clear, both early and late complications are significant. Unfortunately, preoperative identification of those patients requiring TPE rather than abdominoperineal or low anterior resection remains poor. Furthermore, recent improvements in techniques for pelvic slings to prevent small bowel entrapment and protection from irradiation or myocutaneous flaps to obliterate the massive dead space are not yet clearly established as preventors of either early or later complications.

IN 1975 ONE OF THE AUTHORS published an experience with pelvic exenteration as a palliative procedure.[1,2] This material, which included five patients with total pelvic exenteration (TPE) for rectal carcinoma, stressed these patient's debilitated, unmanageable state, which was associated with such bulky tumors. A recent 2-year experience with five more patients needing TPE for rectal cancer uncovered some reluctance to apply the principles of ultraradical surgery to rectal carcinoma especially as primary therapy even with less sick patients. This dichotomy lead to a review of the Vanderbilt experience with TPE for rectal cancer. These data plus an assessment of the factors necessary to determine if TPE is reasonable surgical therapy for rectal carcinoma are the basis for this report.

From the Department of Surgery, VA Medical Center, and Vanderbilt University, Nashville, Tennessee

Materials and Methods

Ten new patients were added to the initial five[1]; all had TPE for rectal cancer. In this review, as well as the literature review, it is possible that some patients whose lesion might have been classified as rectosigmoid by some (higher than 15 cm from the anal verge) are included because they were listed as rectal carcinoma. However, no patient whose lesion was sigmoidal or colonic is included. Thirteen of the 15 patients were males, the average age was 57.6 years, and there were no operative deaths. The information is best analyzed as two groups; the ten patients with one operation (their TPE) and five patients with one or more operations before their TPE (Table 1). In the first group (Group A) one patient had TPE for palliation because peritoneal implants were present and the other nine had curative resections. There were two patients with early complications (two wound infections and one conduit fistula) and four patients with late complications (two colostomy difficulties and two small bowel obstructions). Four patients are alive with no evidence of recurrence (NED) 15 years, 7 years, 34 months, and 16 months post-TPE. The palliative patient when last evaluated at 15 months was alive but had further evidence of visceral recurrence. In contrast, the five patients of Group B with at least one operation before their TPE, all had early postoperative complications (three wound infection, two abdominal abscess, three conduit leak, and two organ failure) and three also had late complications (one colostomy difficulty and two perineal problems). Two patients are alive without evidence of recurrence at 24 and 36 months. In Group B two patients were operated upon for recurrence: one 32 months after low anterior resection with negative nodal disease with postoperative

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radiation therapy and one 9 months after resection for perforated cancer with postoperative irradiation. There were four patients who had early reoperation: one after colostomy to relieve acute obstruction, two after recent explorations during which attempts at *en bloc* resection failed (one of these is also in the recurrent group so the TPE was the third operation), and one because the possibility for a more extensive but curative operation was considered moot.

Assessment of their pathologic stage was especially instructive. The initial belief was that all patients had secure histologic evidence of organ invasion. Because of the well-known variation in the manner by which invasion of an adjacent organ with rectal carcinoma is staged, especially when lymph nodes are negative,[3,4] the details of the pathologic reports were reviewed. Detailed review of the 14 available protocols (the patient who is 15 years postoperative had only conclusions available) showed that in three patients there was histologic evidence of invasion close to the adjacent organ but not into this organ, namely, tumor not inflammatory reaction in the capsule or in adhesions to the organ. In each of these three cases histologic invasion well beyond the immediate perirectal material was present. Figure 1 summarizes these data. Only one patient had known residual cancer postoperatively, and this patient was one of two with positive nodes from the 11 patients with positive organ involvement. In contrast, two of three patients from the close group had positive nodes. Yet all three of the close group are alive without evidence of recurrence whereas only four of the 11 are similar and all these are from the negative node group.

Two patients, both from group B, had had prior radiation therapy (RT). One female had been treated 3 years prior to the present surgical therapy for perforated carcinoma with resection and full postoperative irradiation. After cystoscopy revealed tumor invasion, an attempt at *en bloc* resection was abandoned and the patient transferred to Vanderbilt. TPE, which was accomplished at early reoperation, removed all gross disease, but the postoperative course was stormy. Recurrence was obvious by 6 months and death occurred at 8 months. The second patient recurred 9 months post-RT after resection for perforated cancer. Another Group B patient began a course of irradiation before he consented to the TPE 2 weeks after his initial procedure. He completed his RT postoperatively even though he had negative nodes and was one of three patients with close organ involvement. He is alive NED 24 months post-TPE. Two additional patients received early postoperative RT. Both were from Group A, one with positive nodes and close organ involvement and the other with negative nodes but positive organ involvement. Both are alive NED 16 and 34 months post-TPE. Yet another patient from Group A with negative nodes but positive organ invasion refused early RT only to recur at 12 months and died at 30 months when delayed RT was not effective. Of nine patients including the one with peritoneal implants who did not receive early postoperative RT, three are alive with NED (15, 7, and 3 years), three are alive with recurrence (15, 16, and 18 months) and three have died all with recurrence (11 months, 18 months, and 9.25 years).

TABLE 1. *TPE for Rectal Carcinoma*

5 Multioperations
  2 for recurrence, 3 for poor staging; all had postoperative complications
  2 are alive NED (24M, 36M)
10 Single operations
  1 for palliation (peritoneal implants)
  2 had early postoperative complications
  4 are alive NED (15Y, 7Y, 34M, 16M)

Data pertain to 15 patients (13 males, two females) (average age: 57.6 years) with no operative mortality rate.

In summary, these 15 patients with extensive local rectal carcinoma had a TPE without an operative mortality rate but with a 30% early complication rate and a 50% late complication experience. Nevertheless, all but one (the female with early recurrence and death) enjoyed at least 10 months of good palliation with an average survival of 38 months. Six including two with positive nodes remain alive with NED (15 years, 7 years, 3 years, 34 months, 24 months, and 16 months).

Results

This attempt to analyze all patients undergoing TPE for rectal carcinoma recorded in English journals uncovered many problems.[1,2,5-34] As mentioned earlier, some patients with rectosigmoid cancer are undoubtedly included in summaries especially in reviews of lower colon, colorectal, or rectosigmoid cancer.[11,13,14,21,28] Occasionally, anterior or posterior exenteration is mixed with TPE. Clearly there is overlap of case material especially where centers updated earlier experience or emphasized different approaches.[1,2,7-11,16-19,29-31,34] Further-

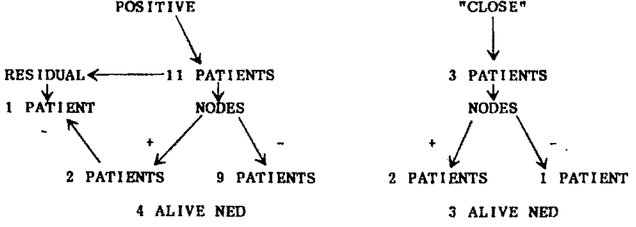

FIG. 1. TPE for rectal carcinomas spread on pathologic staging (14 patients).

TABLE 2. *TPE for Rectal Carcinoma: Study Review*

Study	Year	N
Prior to 1980		
Appleby[5]	1950	6
Brintnall and Flocks[6]	1950	6
Brunschwig and Daniel[7]	1948–1960	15
Bricker et al.[8–10]	1950–1967	43
Eckhauser et al.[12]	1979	10
Total		80
Recent		
Lopez et al.[11]	1987	24
Ledesma et al.[13]	1981	8
Boey et al.[14]	1981	26
McGlone et al.[15]	1982	5
Takagi et al.[16,17]	1986	18
Pearlman et al.[20]	1987	18
Benotti et al.[18]	1987	8
Wanebo et al.[33]	1987	7
Miscellaneous[21–24]	1980	8
Present series	1987	15
Total		137

more, there are reports that must contain acceptable cases,[25–28] but details are not clear enough for their cases to be included in this summary even when others have used their data.[11] Finally, because some include TPE even while extending the procedure further as with sacral resection,[17,20] others may have acceptable patients within their more radical surgical treatment groups.[32,33] Review has been further complicated by grouping colon with rectum or PE with TPE when data on staging, nodal or organ involvement, operative mortality rate, complication rate, or even survival data is provided. Taking into account all of these conditions, Table 2 lists 217 cases of TPE for rectal carcinoma. Although these data may contain a few overlapping patients,[10,11] it is more likely that some with TPE are missing (as many as 22 patients).[11,25,27] As noted later, such inconsistency in case material may not be critical because only trends can be established because of other variability.

While 53 of these 217 cannot be labeled accurately,[7,8,13,21,22] 54 were done for recurrent cancer.[11,17,18,20,22,24,33] These latter include 25 patients who had removal of bone as well as TPE.[7,11,17,10,33] This leaves 110 patients treated for locally advanced rectal carcinoma with a TPE as the primary surgical procedure.[5,6,7,10–12,14–16]

While early series with large numbers of pelvic exenterations reported operative mortality rate near 15%,[7,9–11] more recent reviews with emphasis upon exenerations for colorectal cancer note series with operative mortalities closer to 10%.[10–13,16] Indeed, most believe current care standards for TPE as the primary operation for rectal cancer that has not been irradiated should produce operative mortality rate below 5%.[1,10,20,25] Early reports of a 45% complication rate[8,9] are paralleled in more recent series[14,15] with the best improvement occurring in relation to urinary conduits and the management of their complications.[2,28,31,35] However, in spite of these formidable surgical problems, all note impressive 5-year survivals that are always over 20%[8,9,12,14] and usually over 35%.[10–13,16] Thus, we are a long way from a procedure which is "only for conjecture, hope and further study."[5]

Discussion

Data from the reported cases of TPE, with or without extension to even more radical procedures such as sacral resection, clearly document both cures and palliation of recurrent rectal carcinoma.[7,11,17,18,20,22,24,32,33] However, most note the very limited potential for any given patient at the point of recurrence especially when there is also irradiation treatment failure. In the largest series[32,33] operation for cure was feasible, even when extensive, in only 24 (39%) of 61 referred highly selected patients. Thus, an apprehensive attitude with lesser surgery as primary treatment reserving the ultraradical procedures for recurrence could be justified only if primary radical (TPE) is not effective. Primary TPE for rectal carcinoma in properly selective patients is very effective treatment.

Few would deny that the immediate outcome for colorectal resection has improved in the past few decades or that resection of rectal carcinoma offers the only possibility of cure. Yet improved survival is not clear.[18,36,37] Furthermore, local recurrence is the most common type of failure.[18,32,38] Local recurrence has been recorded in over 50% of cases in many series. Indeed, in reviews involving 1329 patients reported in the 1980s an average of local only (not as part of diffuse disease) recurrence of 15.4% (9–24% range) was found.[18] Because local recurrence can be equated to lower rectum and tumor through the wall, it is not surprising that local recurrence of 30–35% with through the wall but negative nodes is worse than that (20–25%) with tumor within the wall but positive (few or close) nodes. Finally, although all agree positive nodes are usually a determinant for local recurrence, they are not the sole factor.[41,42] With low anterior resection, local recurrence was similar for those with negative nodes[41,47] and those with positive nodes.[45–51] Furthermore, size is not a determinant of recurrence (unless gross tumor is left as residual) or survival.[13] The prognostic implications of rectal wall penetration by tumor, nodal spread, or direct invasion of other tissues and organs that are at the heart of many current discussions about staging systems[3,4,38–41] highlight the dilemma about surgical techniques. When results for lesions penetrating bowel wall but not involving metastatic nodes are no better than those seen with mucosal lesions that have positive nodes, as is the case for rectal cancer,[37-43] concern about more extensive local therapy follows naturally.[15,40-45] When this concern is compounded by considering even more local spread, invasion to adhesions or adjacent organs, as is appropriate for discussion of TPE as primary therapy, the data become less clear because some stage this as distant metastatic disease (Dukes' D[38] or even D_1[34]) while others consider it as local disease (B_3).[39,42] Comparison of cases with invasion to adjacent organs is difficult if not impossible with such variation in the standard staging systems.[3,4]

Carcinomatous extension to adjacent tissues or organs is an important concern because it occurs in 5–10% of colorectal cases.[13-15,21,36,38] The need to remove an organ that is grossly and microscopically invaded if one is to cure cancer is easily grasped and often acted upon. However, more subtle findings cause confusion. Adjacent organ involvement is an independent variable for survival,[4,36,39,44] and pathologically proven tumor penetration has a significantly poorer prognosis than clinical but not pathologic invasions.[21] The latter is termed close. Perhaps most importantly, only 40% of the adhesions at the interface of tumor and adjacent structure are caused by inflammatory response[21,36] or even by an abscess[16] so the remaining majority (77%[14], 66%[15,21]) are tumor bearing. Perhaps these variables explain the wide divergence of TPE from 1.6%[11] to 4.7%.[14] They certainly should contribute to the often noted feature of rectal cancer, local recurrence without evidence for systemic disease.[36-38,41,42] The role of venous, neural, or lymphatic infiltration in the absence of organ, adhesions, or nodal disease is unclear but probably also contributes to unexpected local recurrence.

Not only must the surgeon be aware that apparent extension of tumor can be either tumor, which if entered will almost certainly lead to recurrence, or inflammation, but the surgeon must also realize that many bulky tumors with established organ invasion will not have nodal metastatsis. For the reported cases of primary TPE where specific information has been provided, 60% had negative nodes.[11-15,20] There is less secure information about organ invasion, but what little is available suggests a 60% pathologically proven infiltration. These data show that there is a population of patients with rectal carcinoma who will have extension of tumor beyond the rectal wall into adjacent organs. In many there will not be nodal spread. Although the adhesions may be dense,[15] they can appear inflammatory but still contain tumors.[21,36] As noted by Brunschwig some time ago, with rectal cancer the majority of patients will be males 77%.[8-12,14,16,17,20,33] Although there may be some evidence for effective chemotherapy and/or radiation therapy,[22] most believe these patients have only one chance for cure, total removal of tumor, TPE.

The authors' experience, as well as that recorded in the literature, shows that some patients require a second operation because neither the patient nor the surgeon are prepared for TPE. Such patients have a higher complication rate and may have both a high local recurrence rate and a poor prognosis. Unfortunately, the individual cases cannot be analyzed for these latter two details, although most series contain such patients who appear to have a poorer long-term outcome. In earlier series, preoperative assessment emphasized metabolic, nutritional, and infection control for patients with obvious locally advanced or recurrent disease.[7-11] Indeed, improved outcome and, therefore, the opportunity for meaningful palliation was attributed to just such a program.[1,2] The more recent cases still included two patients with recurrence and one patient with late stage disease, but the others were not debilitated and unmanageable. It is not clear if similar experience is occurring elsewhere. When the patient is less obviously harboring a bulky locally advanced lesion, the opportunity for both patient and surgeon to be unprepared for TPE increases. The hope that newer preoperative tests including computed tomography (CT) or ultrasound (US) would permit better staging has not materialized. Although some stress the importance of these tests,[17,29,30-33,46-49] others believe CT may be no more reliable than digital examination.[47] Data for endosonography[50] in locally advanced rectal lesions is not available, but invasion beyond muscularis propria or into lymph nodes can be detected. Other special tests such as cystoscopy[48] or even lymphoscintigraphy[49] are not obtained as routine evaluation.

Thus, the properly selected patient in this thesis is one whose rectal carcinoma at the time of initial evaluation has direct invasion into adjacent organs such as bladder, prostrate, or seminal vesicle but whose nodal metastasis is minimal and localized in the pelvis if present at all. While some patients may have such advanced local disease because of neglect,[1,14] concern should occur with all bulky or fixed tumors. Most will be males with these findings assessed by routine physical examination.[36,45,46] Unfortunately, CT and US may not improve either sensitivity or specificity. The surgeon needs good clinical suspicion if preoperative plans, which are essential as well as extensive for both the patient and for special operative techniques, are to be correct. Because intraoperative decisions can be difficult and insecure, the indecision about the need for TPE gets compounded.

The conduct of the TPE operation follows the principles championed by Brunschwig and Daniel[7] with the refinements, especially for urinary diversion, established by others.[8-10] When cure is possible, the wide margins not only extend laterally[11-20,25-28,36,37] but also encompasses the mesorectum,[53] local nodes[40] including unrecognized small (0.5-m) ones,[54] and pelvic adhesions.[14-16,21,36,37,41,42,44,45,51,52,57] Furthermore, when such extensive procedures are planned, there is less chance for compromise on distal margins.[51,55,56] Wide perineal resection is possible for very low lesions just as establishment of bowel continuity is for the higher lesion.[10,14] Rarely is resection of bone[7] including sacrum appropriate.[11,17,20,33] The goal is the removal of all central tumor mass regardless of its size because neither cure nor good palliation occurs if residual tumor exists.[1,11,14,16,20] Reconstruction usually involves an ileal loop,[8-18,25-28,35] but it may use a jejunal loop,[2] sigmoid conduit diversion, or even the newer continent urinary diversion procedures.[35] When these procedures are being done for recurrent tumor or for radiation failures, disappointing experiences,[10] most believe that extensive lateral wall dissection is not warranted both because it increases the complication rate and because when positive nodes are found neither cure not palliation follows.[1] However, newer techniques especially those with myocutaneous flaps may change this attitude.[19,20,31-33]

Concern about control of the massive dead space left within the pelvis after TPE initially centered on prevention of early infection and late small bowel obstruction.[8-11] Thus, efforts were made to fill the defect with omentum[58] or to prevent small bowel entrapment with perioneal and/or omental slings. More recent emphasis has been on mesh slings,[59-61] especially absorbably ones that could keep the small bowel out of the pelvis during early postoperative RT. After experimental success,[59,60] Devereux et al., who has used polyglycolic acid mesh in 60 patients, noted the need to place the mesh at the level of the umbilicus, thus depending upon absorption later to decompress the abdominal contents. Devereux et al.[59,60] reoperated upon six patients (as in two patients in this study) months after the sling was placed finding no residual mesh as well as no evidence for infection. Neither the uses of balloons, breast prosthesis, or the like within the pelvic space nor the use of an absorbable mesh address the issue of late small bowel obstruction. Use of myocutaneous flaps to close defects especially after irradiation failure has suggested yet another way to deal with both perineal closure and obliteration of pelvic death space.[19,20,25,32,33,63-65] The possibilities include rectus, gluteal, or thigh myocutaneous procedures as well as bilateral tensor fascia lata grafts. Clearly these should be utilized during the primary operation.[19] Thus, they need to be planned for preoperatively. Their use has controlled sepsis, fistula, and perineal problems, but data to show improvement in small bowel obstruction are not yet available.

Preoperative radiation therapy impacts upon these patients in two ways[67-70]: (1) when given immediately preoperatively it may increase the operative complications[35] but it is also possible that it can downstage the tumor to make it operable[69] and (2) to make a lesser operation feasible.[22,70] While almost every review notes or comments upon an increased complication rate in previously irradiated patients or justifies newer procedures such as myocutaneous flaps to improve results, detailed analysis is not feasible given the way data are presented. The arguments about the value of postoperative radiation for patients with TPE for rectal cancer parallel those currently occurring for colorectal carcinoma with low anterior resection or abdominoperineal resection. Because analyzable data are not available, this is not discussed further.

The second part of this thesis requires the TPE to be effective therapy, that is, it must be able to be done safely and produce good results. As noted when all reported cases were summarized, the operation can be accomplished with under 10% mortality rate,[10-13,16,18] but with significant complications. If one emphasizes primary TPE as the first operation being well planned for newer surgical techniques in fit patients who have not had prior pelvic radiation, both of these figures improve significantly. The cures, which are regularly over 20%[8,9,12,14] and often over 35% at 5 years,[10-13,16] are more than would be anticipated with more local resection and postoperative RT for the residual disease. This latter is the only available alternate to TPE for all of these patients with the possible exception of the few with both negative nodes and only close organ invasion. This small group is almost impossible to define with methods used today. Most grant that even when cure does not occur this procedure offers significant palliation.[1,11,14,16-18,20,23] When recurrence occurred, it was often 10 or more months post-TPE (10 months[14], 20 months[11], always after 10 months in this series) becoming manifest 4–8 months before death. Many have noted the absence of symptomatic pelvic recurrence[1,14,16] even with visceral spread or carcinomatosis. This later feature is very different from the course of recurrence in lesser operations.[38,52]

Based upon this experience and the review of data available, TPE as primary therapy for rectal carcinoma should be applied in selected patients. It offers both the only chance for cure and a reasonable potential for palliation when no gross tumor is left. Newer techniques and improved management both before and after operation have made the procedure safer, but future improvement in dead space management is necessary. Unfortunately, preoperative staging remains poor especially for selecting these patients from others who need a lesser procedure. Only an alert surgeon willing to consider TPE as primary therapy can fill this critical gap.

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DISCUSSION

DR. WILLIAM D. JOHNSTON: I appreciate Dr. Williams's giving me a copy of his manuscript to review.

You have heard a very erudite presentation of a very difficult problem, and when you have a chance to read the manuscript, you will also be convinced that they have really milked all of the data to try to come up with solid information on which to base several difficult decisions. Those difficult decisions, as I see them, can be summarized as falling into four categories. First, the difficulty of preoperative assessment; second, the difficulty of intraoperative assessment toward making the decision of what operation to do; third, whether or not you are going to use postoperative radiation therapy; and fourth, what to do about the pelvic dead space.

I am going to comment on my present approach to each of these four problems, and I welcome your response of what you, Dr. Williams, and those who choose to discuss this paper do. I believe, as you have shown with your data, that the pelvic (vaginal and rectal) exam is the most important preoperative test towards assessing the local extension of tumor. CT scans and MRI are helpful when they show evidence for positive distant metastasis. However, in the absence of distant metastasis, it is important to determine preoperatively the local extent of cancer in the pelvis, and we believe that we can do this best when the patient is under anesthesia during the pelvic exam. We usually do this using general anesthesia at a date prior to the date of the planned resection. However, if you are going to do the exam at the same time of your definitive operation, I think you should have the patient and his family, prepared for the possibility that you are going to do a total pelvic exenteration. This would mean having the patient educated by yourself and the stomal therapist, and having the location of both stomas marked on the skin in the proper position.

Secondly, what do you do after you have begun operating on a patient whose pelvic exam indicated the likelihood of needing to do a total pelvic exenteration. The pelvic dissection doesn't start until you are reasonably certain that there is no metastasis outside of the pelvis. After you are certain of that, the pelvic dissection should start along both common iliac vessels and extend down the external iliac vessels, and then extend posteriorly into the obturator fossa, down to the internal iliac vessels with medial mobilization of the ureters and while mobilizing the bladder away from the pubic bone. By not transecting the ureters or any of the blood supply up until this point, all of this can be done prior to making any commitment to proceed with the pelvic exenteration. At this point, you can squeeze from both sides to try to assess the presence of tumor between the anterior wall of the rectum and the prostate and/or the posterior trigone of the bladder in a male, or between tumor extension into the cervix, vagina, or uterus in a female, without extension into the urinary bladder to allow a posterior exenteration, without resection of the urinary bladder in addition. Even with all this dissection in preparation of making a commitment, the decision is still difficult to make; but you are giving yourself the best opportunity to make the right decision by doing this much dissection before committing yourself by transecting the ureters and the blood supply to the pelvic viscera. If a fibrotic extension is proceeding laterally from the area of the anterior rectal wall and prostate or trigone of the bladder, then I believe that you should proceed with a pelvic exenteration, rather than hope that the fibrotic reaction is not due to cancer. If this amount of dissection should prove that there is a good plane between the anterior rectal wall and the prostate or bladder, then I would proceed with making an incision through the peritoneum at that point and dissect down between the bladder and the rectum until I reach a fibrotic reaction. If I were to reach a dense fibrotic reaction including the trigone of the bladder or the prostate gland, then I believe that this would indicate a total pelvic exenteration. Dr. Williams's assessment of the data confirms that it is very difficult to tell whether or not there is cancer in this location, but I think it is better to resect adequately than to find out postoperatively that tumor has been transected in the process of trying to do an abdominal perineal resection, when a total pelvic exenteration should have been done.

Thirdly, what do you do about radiation therapy. If our preoperative assessment reveals a primary operable case to be curable by total pelvic exenteration, we tend not to use preoperative radiation therapy, but to wait until all the histology is completed on the operative specimen and to use postoperative radiation therapy after total pelvic exenteration if there are multiple lymph nodes positive, or if there are lymphatic extensions or perineural or perivascular microscopic extensions beyond the primary tumor.

Fourthly, what do we do about the pelvic dead space. Just as Dr. Williams has pointed out, it is very important to fill the dead space with something other than small bowel to help prevent entrapment and obstruction and other complications regarding the small bowel. I most frequently fill it with omentum when it is adequate. However, quite often it is not adequate, and I call on the help of a plastic surgeon to consider a myocutaneous flap first; I think one of the most helpful flaps in this situation is the rectus abdominis myocutaneous flap based on the inferior epigastric vessels. The surgeon doing the resection will have to be careful not to transect the inferior epigastric vessels, which can be done without compromising the pelvic dissection.

Leaving the pelvic cavity filled with something other than small bowel aids greatly in reducing the complications that can result from postoperative radiation therapy. It is also important that the radiotherapist use multiple fields and multiple positions of the patient to try to avoid excessive dosage to any area of small bowel.

I appreciate your asking me to discuss this paper and providing me with the manuscript ahead of time. I commend you on an excellent and thorough coverage of the difficulties concerning the question of total pelvic exenteration for rectal cancer.

DR. MAURICE J. JURKIEWICZ (Atlanta, Georgia): First of all, may I compliment Dr. Williams on a very nice presentation and a superb paper. I want to thank him for providing me with an advance copy. Not only did I learn a great deal from it, but it also gave me a little feeling of a déjà vu. When I was a resident, I participated in these 43 cases done by Dr. Bricker and his colleagues, Harvey Butcher and Allen McAffee. I remember all of the things that we went through in an effort to prevent the immediate complication of small bowel obstruction.

I rise to comment on what has been termed the pelvic dead space. May I call your attention to a principle articulated by Allen Kanavel in the 1920's and published in SG & O. Kanavel called attention to the principles involved in the treatment of wounds with noncallapsing walls. Examples include empyema and chronic osteomyelitis, as well as the pelvic dead space referred to by Dr. Williams. Kanavel pointed out that for healing to occur, the wound surfaces have to be in contact. If such contact is prevented by bony walls as in empyema, chronic osteomyelitis of the femur or tibia, or the case of the bony pelvis, then another strategy is indicated.

Kanavel advocated the use of muscle flaps to accomplish the desired contact of tissues so that healing could occur.

Radiation treatment of patients with rectal cancer adds another dimension to the problem of pelvic dead space. I would submit that the sling, although attractive in concept, would do little for the problems attendant upon preoperative irradiation.

Our experience is with the chronic wound and not the acute.

(Slide) We have treated 24 patients, 16 of which had a persistent perineal sinus following proctocolectomy for Crohn's disease. In those patients, we initially used gracilis to fill the pelvic dead space. We had failure in three, a figure consistent with the scanty literature on the problem.

Gracilis is a difficult muscle to use. It is a long muscle, and it doesn't provide quite enough tissue for what you want it to do. Therefore we turned the gluteus. In those patients, (13 in all;) we had no failures with the pelvic wound. We treated the three patients in whom the gracilis failed by a secondary procedure with the gluteus. All three patients are now healed.

More importantly, and pertinent to this discussion, however, are those patients who had radiation for rectal carcinoma follwed by radical abdomino perineal resection. In eight such patients treated with gluteus there were no failures whatsoever. We had to supplement the gluteus in three with gracilis or rectus abdominis to adequately fill the pelvic dead space.

There is no question in my mind that one can create a living pelvic diaphragm and fill the dead space at the same time. A combination of muscles may be necessary. I would agree with Dr. Johnston that the rectus abdominis muscle provides the best possibility for the reconstruction of a living pelvic diaphragm.

Leonard Miller, formerly one of our residents, is working with Glenn Steele at the New England Deaconess Hospital. He has been using a flap of entire posterior skin of the thigh, de-epitheliazed to fill the pelvic dead space and to recreate the pelvic diaphragm. This flap is based on a branch of the inferior gluteal artery.

In my opinion, muscle flaps have made a real contribution to the decreased morbidity in patients similar to those described by Dr. Williams.

DR. CLIFFORD WHEELESS (Baltimore, Maryland): I would like to thank my host, Dr. James Arnold of Baltimore, and the Southern Surgical Association for the privilege of attending this meeting and the opportunity to discuss this excellent paper by Dr. Williams and his colleagues from Nashville. The paper was thoroughly prepared. The authors are to be commended on the clarity of their presentation.

We might now consider that Phase I in total pelvic exenteration for selected cases has been accomplished, as has been so ably reported to you today.

We believe that we have now entered Phase II of total pelvic exenteration, namely, the emphasis on improvement of quality of life for these unfortunate patients.

There are three quality of life procedures that are now under current development. Dr. Williams has mentioned two of them.

(Slide) The first quality of life procedure is an alternative to urinary diversion by the Ileal Loop (Bricker Bladder) by performing a continent urostomy, such as the nonrefluxing Koch's pouch.

(Slide) The second quality of life procedure is an alternative to End Sigmoid colostomy, when adequate cancer surgery allows a sphincter-saving procedure by performing a low coloproctostomy ultilizing a low pressure reservoir of detubularized colon, such as the rectal "J" pouch with a Strassburg-Baker anastomosis.

The above two techniques offer the possibility of elimination of ostomy bags from the abdomen.

(Slide) A third quality of life procedure in females is the construction of a Neo Vagina by using the risidua of the Omental "J" flap. The blood supply for the flap is based on the left epigastro epiploic artery. Traditionally, the flap has been used to close off the pelvic inlet. We have found the flap useful in constructing a cylinder that can be sutured to the vaginal introitus and lined with a split thickness skin graft.

My question to the authors: Is there any consideration for these procedures in this series of patients?

DR. BENTON M. HILBUN (Tupelo, Mississippi): During my training period under Dr. Hardy, we were taught that rectal carcinomas should be treated with radical surgery and that the only chance for cure was total surgical excision.

This continued in my practice for the first ten years or so, and although the number of cases of this nature that have come to my care have been limited, in this manner we have continued to do a total surgical excision, often in conjunction with the urologist, and in some cases, a gynecologist.

However, in the last year or two, influenced perhaps, by the chemotherapist and the radiation oncologist, I have felt somewhat guilty about proceeding with such a radical procedure, and we have been influenced to use preoperative radiation and chemotherapy, rather than initial surgical excision.

I want to thank Dr. Williams for reinforcing the concept of initial excision. It gives me some confidence to go ahead with this radical surgery, when I have, in the last year or two, felt somewhat guilty about it.

I have one question for Dr. Williams. If, at the time of laparotomy, unsuspected liver metastases were found, would he still continue with the total pelvic exenteration, and would he consider intra-arterial hepatic fusion of 5-FUDR postoperatively?

DR. ROBERT E. CONDON (Milwaukee, Wisconsin): It seems to me that the crux of this problem is the large bulky, truly low-lying rectal carcinoma, a sort of carcinoma that no single surgeon sees in any great number over any reasonable period of time; so the first caveat I must give you is that my remarks are based on a relatively limited personal experience.

Second, it seems to me that within the total spectrum of patients who have such tumors, defining the need for pelvic exenteration is relatively straightforward, given the assistance of CT examination and the use of knowledgeable digital and manual examination in those patients. But there is one subset within the spectrum of patients where I don't believe those modalities are always sufficient; at least in my experience they are not. That is the male with a bulky anterior rectal tumor where the issue is: Has it invaded the prostate, the seminal vesicles, or the base of the bladder? If it hasn't, obviously the tumor can be excised without incurring the disability that is associated with pelvic exenteration.

On the other hand, it is a major disaster for the patient to blunder into a tumor while dissecting the plane below the bladder and anterior to the rectum, since that sets the stage for pelvic and perineal recurrence, which is not easy for any of us to manage successfully.

In approaching this problem, therefore, I have for some years used radiation therapy, directed not so much at improving the long-term prognosis, but at reducing the bulk of the tumor and making a definitive judgment about the need for pelvic exenteration somewhat easier to make.

To the consternation of my radiation colleagues, I operate on these patients as soon as they have completed a full course, usually of 6,000 rads or so of irradiation, and have not waited the traditional 6 to 8 weeks afterwards, because at that early stage you don't run into some of the secondary radiation effects that increase the difficulty of pelvic dissection.

More recently, I have been impressed by my urology colleagues with the real utility of using transanal ultrasound examination. It grows out of their use of this modality to examine the prostate, but has been helpful in adding to the body of knowledge that allows you to make a judgment about whether, in fact, that crucial plane anterior to the rectum is involved with tumor or not.

Les, it seemed to me that you indicated you were always able to arrive at these judgments with confidence using only your finger. My finger is not so sensitive. I wonder if you can give me some advice about how to increase its sensitivity.

DR. HIRAM C. POLK, JR. (Louisville, Kentucky): I rise to make three different emphases from our essayists.

I think that, first of all, you have done us a good service by bringing this to our attention. It is obvious that there are literally hundreds of patients who have been rendered well from this operation, and who have not been reported in a long time basically because it is an operation that has been a standard procedure now for more than 20 years.

I think what happens is that we do lose sight of the operation's utility, and periodically it is very valuable for all of us to be reminded of its utility. Certainly it accomplishes exactly what you have described: low mortality and morbidity, always under 10%, nearly a 40% cure of the cancer forever in every patient.

Two emphases that are different than yours:

We see many more women requiring this operation than you have indicated. Women have often had hysterectomy earlier in their life, and then develop a rectosigmoidal tumor which develops bladder invasion. She is quite a suitable candidate. I think Dr. Wheeless obviously reflects that in his comments, in the sense that they are amendable to re-resection, and indeed, a little bit easier.

The third point, about how to pick these patients out has been written down a number of times, I think, and is a paradox but a useful hint. That is the work that Spratt[1] describes so clearly in talking about the large bulky nonmetastasizing variant of colon cancer. If you have a large tumor that is free of liver metastases, you begin to think that is an ideal case to work on, because not only is it going to be free of liver metastases, but, more often than not, it is going to be free of nodal metastases. Paradoxically, it is the big tumor that is more amenable to this kind of treatment. It needs the treatment more, but don't let the size of the thing make you back off, because truthfully, I think those are the patients who are ultimately the most likely to be helped by this.

You have done us a service by emphasizing this, and I appreciate the paper.

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DR. L. F. WILLIAMS (Closing discussion): Let me thank all the discussants and attempt (for the sake of time) to cover the highlights in reverse order.

As always, Dr. Polk has pointed out important observations from the past. In fact, the very patient who has the big bulky tumor and does not have metastatic disease is the person we are talking about. The reason I emphasized the digital examination was only because the current literature, Dr. Condon, is so heavily weighted toward everything else. In fact, it is still possible to make this "guess" by digital exam, and you yourself know that I am certain. It may be true that the intrarectal ultrasound is more sensitive than we have known.

I don't know why there weren't more females reported, Hiram, but I suspect it was from my emphasis on this as a primary treatment rather than as therapy for recurrent disease. We may have excluded some women who might well have had TPE, but I did not run across the observation that you offered.

What to do in the presence of liver metastases? We defined this as pallative, that is no longer a patient available for cure, but as we reported in 1976, in selected patients with big, bulky tumors, foul smelling fistula and the like, TPE provided reasonable palliation. Thus, I might well do a TPE if I found liver metastases in such a patient.

The rest of the discussions actually related to experiences from the series that I reviewed. For the sake of time, I would point out that the new techniques include myocutaneous flaps for reconstructions, and ways to prevent ostomies.

Is it still true, however, that many patients may be treated by surgeons who don't realize that TPE is a reasonable operation, with the patient thereby missing the chance for cure? We need to pick out those patients.

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3. Thrombostat solution of the desired strength is prepared and the pump sprayer cap inserted and seated on the Thrombostat solution vial. Note: Several strokes of the pump sprayer will be required before the Thrombostat solution is expelled.
4. Alternatively, when Thrombostat in dry form is needed, the vial is opened as described above and the dried Thrombostat broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.

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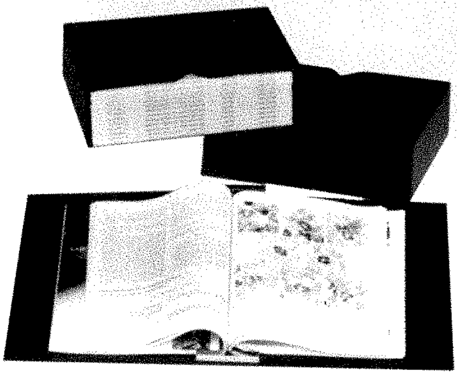

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Factors Improving Survival in Multisystem Trauma Patients

JOSEPH A. MOYLAN, M.D., KEVIN T. FITZPATRICK, P.A.-C., A. JAMES BEYER III, and GREGORY S. GEORGIADE, M.D.

From Duke University Medical Center, Durham, North Carolina

This report analyzes the effect of air *versus* ground interhospital transport on survival following multisystem injury. There were 136 air-transported patients *versus* 194 ground-transported patients. The groups were similar in trauma scores, ages, mechanism of injury, and organ systems injured. There was a statistically significant survival advantage for air-transported patients with trauma scores between 10 and 5 (82.8% survival *vs.* 53.5%, p = < 0.001). The time interval between accident and admission to the authors' institution was similar for both groups. Important therapeutic interventions contributing to better survival by the air-transported group included higher incidences of endotracheal intubation (50% *vs.* 25%), blood transfusions (32% *vs.* 10%), larger volumes of electrolyte fluid (3.3 L per patient *vs.* 2.1 L per patient) as well as the use of MAST trousers (60.3% *vs.* 34.9%). Transport charges for both ground and air services were similar. However, helicopter charges met only 15% of the operational budget of the aeromedical service. The remainder of the costs were generated from hospital patient revenues. Overall, total hospital charges were similar for both groups and were influenced by the variability of length of stay, particularly for orthopedic patients.

MORTALITY RATES from major trauma have been shown to be significantly improved by rapid access to definitive care, particularly during the "golden hour" following injury. Many variables affect mortality rate during the initial phase of care including the availability of highly trained emergency medical technicians (EMTs) to care for the trauma patient both at the scene and during transport, as well as the specialized health care personnel and resources available at trauma centers. During wartime the helicopter has been instrumental in improving survival by providing rapid transport of the injured soldier to medical care.[1] The role of the helicopter in civilian trauma continues to be questioned.

There are two missions for aeromedical transport: scene response and interhospital transportation.[2] Reports from helicopter-based services show that advanced trauma life-support procedures were performed frequently at the scene of accidents with low morbidity rates.[3] However, only a single report comparing air *versus* ground transportation shows better survival for trauma patients treated and transported by helicopter from the scene of the accident.[4] In rural states, the majority of patients treated at major trauma centers have their initial medical treatment begun at an emergency department nearest to the scene of the accident and are then referred to the trauma center. In this type of trauma practice, the helicopter is most frequently used to transport critically injured patients from outlying hospitals to a tertiary trauma facility. The focus of this study is the comparison of the impact of helicopter *versus* ground ambulance on interhospital transportation of severely injured patients.

Methods

All patients with trauma scores of 12 or less, excluding local accident victims, admitted to the Duke University Medical Center Trauma Service beginning in 1985 were separated into either helicopter or ground transport groups and matched by trauma score comparing mechanisms of injury, age, systems traumatized, Glasgow scores, and mortality rate. Patients with complete referring hospital and transport records were reviewed to compare changes in physiologic status during transport and interventions prior to arriving at Duke Medical Center, which may have affected outcome in both groups. Ambulance charges, helicopter charges, and costs as well as total hospital charges were also evaluated for the air and ground groups.

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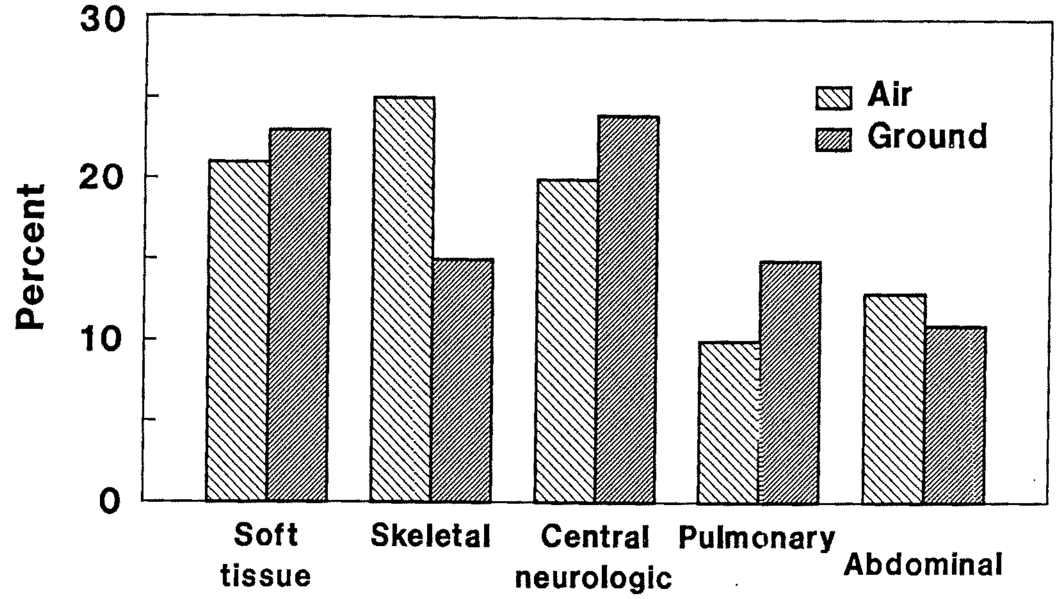

FIG. 1. Systems analysis of air- *versus* ground-transported patients.

Results

Records of 330 patients with trauma scores of 12 or less admitted to the Duke Trauma Service were reviewed. One hundred thirty-six patients were transported by helicopter while 194 patients were transported by ground ambulance. The air group had a mean age of 31.4 years and a mean trauma score of 8.7, while the ground group had a mean age of 33.4 years and a mean trauma score of 9.2. Glasgow coma scores were 8.6 for the air group *versus* 10.6 for the ground group. In the ground group 76% were injured in motor vehicle or industrial accidents and the remainder were assault victims. Of patients transported by helicopter, 85% incurred motor vehicle or industrial trauma while 15% were assault victims. The frequency of organ systems injured are shown in Figure 1. The average number of organs injured per patient was 1.9 for the ground group and 2.1 for the air group. Overall survival rates by trauma score are shown in Table 1. A statistically significant survival advantage for air transport was documented for patients with trauma scores between 10 and 5. In this group, there were 101 ambulance transport and 64 helicopter transport patients with a survival rate of 53.5% (54 of 101) and 82.8% (53 of 64), respectively (p = <0.001). Mean trauma scores for nonsurvivors was 4.1 for the air group and 7 for the ground group.

TABLE 1. *Overall Survival*

Trauma Score	Air	Ground
12–10	78 (97.4)	92 (92.3)
9–7	16 (81.3)	46 (47)
6–4	19 (63)	36 (27)
3–0	23 (15)	20 (5)
Total	136 (89)	194 (61)

Percentages are given in parentheses.

Ninety-six patients of 194 transported by ground had complete referring hospital and ambulance records, which were compared to the records of 136 air-transported patients to define important parameters affecting improved survival in the helicopter group. In this subset, 23% of the ground group were assault victims *versus* 15% in the helicopter group. Mean ages and trauma scores were comparable (13.4 air *vs.* 30.6 ground and 8.7 air *vs.* 9.2 ground). Systems injured analyses are shown in Figure 2. The average number of systems injured per patient were 2.1 for the air group and 2.2 for the ground group. Survival rates for each trauma score grouping were similar to the overall group (Table 2).

Therapeutic interventions prior to arrival at the hospital for each type of interhospital transport are shown in Table 3. Of the 46 patients aerovacuated to the hospital requiring urgent blood transfusions, 40 had their units started by the flight team at the referring hospital or during transport. Only ten (10.5%) of the ambulance group transported from outlying hospitals received blood prior to arrival at the hospital, although 26% of the ground group required blood urgently upon arrival at the Duke Emergency Department. Sixty of 68 patients (88%) in the helicopter transport group requiring airway intubation had their endotracheal tubes placed under the direction of the flight team at the referring hospital or in transport. Only 11 of 24 ground transport patients (47%) requiring urgent endotracheal intubation were intubated prior to arriving at the hospital. The remaining 13 patients required emergency endotracheal intubation by the hospital's trauma service due to airway complications. No patient in the air transport group had deterioration in their vital signs during the transport

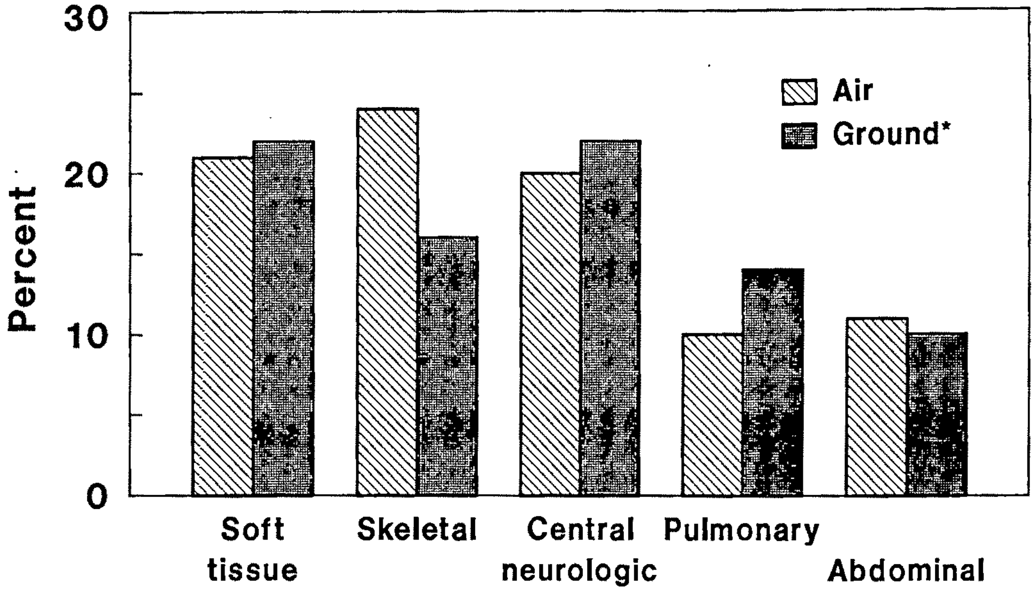

FIG. 2. Systems analysis of multisystem trauma patients.

phase between the referring hospital and Duke while 43% of the ground transport group became hemodynamically unstable. The average total time from occurrence of injury to arrival at the hospital was slightly longer for the air group (182 minutes *vs.* 175 minutes).

Transport charges for both types of services included a base charge plus a per mileage fee, which were billed to the patients. Life Flight helicopter charges averaged 15% more than the ground ambulance; however, the charges for helicopter service covers only 15% of the operational cost. Ground ambulance organizations were able to operate with a balanced budget or are dependent on local charitable donations. Total hospital charges were similar for both groups ($26,000 ground *vs.* $23,858 air). Separation of charges by trauma scores were also similar: trauma scores of 1–4 ($23,717 air *vs.* $30,965 ground); trauma scores 5–8 ($22,828 air *vs.* $24,863 ground); trauma scores 9–12 ($21,525 air *vs.* $19,603 ground).

Discussion

Survival following multisystem injury has improved over the past decade with the development of organized emergency medical service systems. Many factors of this system including designation of trauma centers, advanced prehospital care, communications systems, and better technology in the treatment of multisystem injury influence these improved statistics. Prehospital services vary from urban areas where paramedic level EMTs provide care to more rural areas which vary from basic EMT to EMT-intermediate level care. The impact of EMT prehospital care on survival is still being evaluated. Alexander et al.[5] showed improved survival from care provided by paramedic level EMTs in motor vehicle trauma patients while Boyd et al.[6] demonstrated no difference in survival between care given by basic or advanced EMTs. The utilization of ground ambulances during wartime was associated with delayed access to initial surgical treatment for the injured soldier. Military experience with helicopters has demonstrated progressively lower mortality rates with serious injury supporting the concept of shorter time intervals between injury and effective surgical care as the important factor in this improved survival.[7] Additional benefits of rapid air transport on the battlefield were lower morbidity rates, improved limb salvage, and shortened hospitalization. Civilian experience with helicopter transport for scene response has not been able to demonstrate survival differences. While many reports attest to the improved level of care provided by flight teams who are trained in Advanced Trauma Life Support and Advanced Cardiac Life Support procedures, the value of this alternate

TABLE 2. *Survival of Patients with Complete Prehospital Records*

Trauma Score	Air	Ground
12–10	78 (97.4)	48 (97.9)
9–7	16 (81.3)	18 (62.5)
6–4	19 (63)	15 (40)
3–0	23 (15)	15 (12)
Total	136 (89)	96 (74)

Percentages are given in parentheses.

TABLE 3. *Interventions*

	Air	Ground
Blood transfusions	32%	10.5%
Intubation	50%	25%
MAST	60.3%	34.9%
Fluid volume prior to arrival	3.34 L/pt	2.1 L/pt

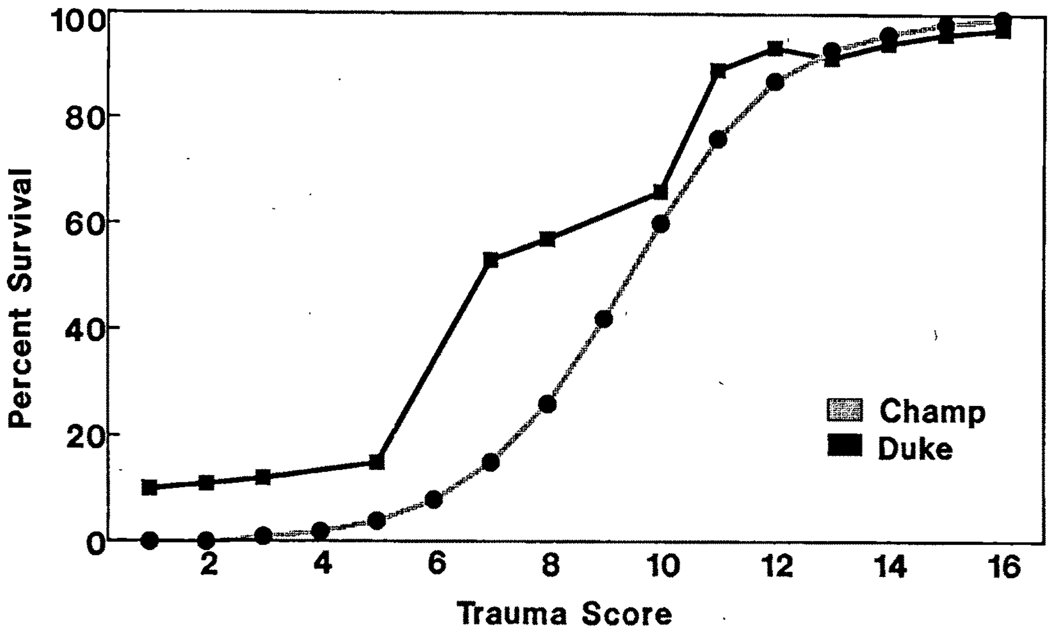

FIG. 3. Duke *versus* Champion[8] predicted survival by trauma score.

method of prehospital transport has been seriously challenged. Only a single report comparing transportation of a large volume of trauma patients from the scene of the injury has shown an improved survival over predicted mortality rate for the air *vs.* ground transportation.[4]

Trauma centers with organized trauma services, outreach educational programs, and trauma registries for outcome analysis provide a multifactorial approach to better trauma care. Level I trauma centers such as Duke University Medical Center, which has a trauma registry containing over 2000 patients, have shown favorable survival statistics compared to the national experience such as shown by Champion[8] (Fig. 3). While the basic principle of triage is to transport the patients with serious multisystem injury to a trauma center, rural states with extensive distances between trauma centers are not suited to this approach. Patients are most commonly taken to the nearest hospital where their initial treatment is provided. Those needing specialized trauma care in a Level I trauma center then require a second transport to the tertiary care center. The rural practice of trauma care is different from that of urban trauma centers with a twofold increase in mortality rates for specific motor vehicle injuries.[9] In this setting the helicopter is utilized primarily for interhospital transportation of critically injured patients rather than scene response.

Duke Trauma Center, centrally located in North Carolina, receives over 75% of multisystem-injured patients shortly after having their treatment begun at other outlying hospitals. With the initiation of the helicopter program, it was possible to compare the impact of air *versus* ground transportation on survival for referred trauma patients. A trauma score of 12 or less was selected for this study because these lower trauma scores reflect serious injuries associated with increased mortality rates. The study group included over 300 air- or ground-transported patients who were similar in age, trauma scores, mechanism of injury, and systems injured. There was significantly better survival advantage for severely injured patients with trauma scores between 10 and 5 who were transported by helicopter. The survival in the midrange trauma scores (10–5) was 82% for the air transport group and 53% for the ground transport group. While there were more survivors with trauma scores of 4 or less in the aerovacuation group, no statistical advantage could be attributed to helicopter transportation because of the small numbers of patients.

Survival for injured patients with trauma scores of 11 or higher was excellent for both groups. There was no advantage for aeromedical transport for these patients. This points out the need for careful triage prior to dispatching the helicopter, especially for busy helicopter programs where availability of the helicopter may be limited.

Lower mean trauma scores for nonsurvivors in the air *versus* the ground transport group is another indicator of the impact of care provided during transport. In order to define the factors influencing improved survival for patients with midrange trauma scores, the hospital records of those ground transport patients with complete documentation to compare to the air transport group were utilized. Approximately one-half of the ground transport group arrived at the Duke emergency department with complete documentation of the accident and treatment received at the referring hospital. The remaining records of the ground ambulance group lacked key information on the treatment prior to admission to the Duke Hospital. This subset of ground-transported patients were similar in terms of types, numbers of organ systems injured per patient, mechanism of trauma, ages, and trauma scores.

The time interval from scene of accident to admission to the hospital was similar for both ground and air transport groups, indicating that other factors are important in improved survival for the aeromedical group. Therapeutic interventions including blood transfusions, endotracheal intubation, and the use of Medical Antishock Trousers were significantly more frequent in the air-transported group. Of patients requiring intubation because of significant head and neck or chest trauma, 88% of the intubations were placed under the direction of the flight team prior to arrival at the hospital. Only 47% of the ground ambulance patients requiring intubation had their endotracheal tubes placed prior to arrival at the hospital. Significantly higher percentages of the air-transported group had blood administered prior to arrival at the hospital under the direction of the flight team. In addition, Medical Antishock trousers were more frequently employed in the air-transported group. The aerovacuated patients received a larger electrolyte resuscitation during transport and prior to arriving at the hospital.

The impact of utilization of the Life Flight personnel with critical care training under direct medical supervision had a beneficial effect in that no patients in the air-transported group had deterioration of their vital signs during the transport phase from the referring hospital compared to 43% of the ground group, which did become more hemodynamically unstable. The Life Flight helicopter program carries O– blood on interhospital transports as well as utilizes any blood that is crossmatched at the referring hospital. The flight personnel are skilled in endotracheal intubation as well as other advanced cardiac and trauma life-support techniques. Ventilatory support including the capability of providing PEEP and continuous suction for chest tubes can be provided during air transport. The availability of constant medical supervision via radio and telemetry made other pharmacologic interventions possible during aeromedical transport including treatment of hemorrhagic or cardiogenic shock, dysrhythmias, or increased intracranial pressure from head injuries.

The charges for the helicopter service billed to the patients were similar to ground charges in the area. The establishment of the charges for the helicopter were determined by many internal factors in the medical center. These charges, however, only met 15% of the operational expenses of the helicopter service. The remainder of the operational costs were generated by revenue from inpatient hospital charges and represents an institutional commitment to trauma care. No difference in hospital charges including breakdown by trauma scores could be found between the two groups. These results may be influenced by variables in length of stay, especially in patients with long bone fractures. A larger series of patients may show a favorable financial impact of the helicopter service on patient care.

In summary, analysis of the Duke experience in the helicopter transport of multisystem trauma patients demonstrates that an organized systems approach to trauma care improves survival. In the rural setting, interhospital helicopter transportation provides a lower mortality rate by the prompt extension of Level I trauma center resources and expertise to the primary care hospital rather than by shortened intervals between injury and admission to the trauma center. Aeromedical transportation provided hemodynamic stability and physiologic support in the resuscitation phase of trauma care. Interhospital helicopter transportation was most beneficial to trauma patients with midrange trauma scores between 10 and 5. While charges generated by helicopter transport do not meet operational expenses, these operational deficits were met from hospital patient revenues associated with improved survival.

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DISCUSSION

DR. BASIL A. PRUITT, JR. (Fort Sam Houston, Texas): Dr. Moylan, Dr. Georgiade, and their colleagues have demonstrated the importance of stratifying patients by injury severity when assessing outcome, and have presented data indicating that a significantly higher percentage of injured patients with trauma scores between 10 and 5 survived when their interhospital transfer to a Level I trauma center was by helicopter as compared to ground ambulance.

These authors have found that time between the injury and the admission to the trauma center was not influenced by the means of transfer, but that the means of transportation influenced the level of prehospital care applied to the patient. That is, endotracheal intubation, application of MAST trousers, infusion of blood, and the rapid infusion of intravenous fluids in general could be carried out by flight team personnel prior to and during the aeromedical transfer.

In short, the earlier application of trauma center-directed care appears to be more important than rapidity of patient movement.

The author's experience mirrors that of the U.S. Army Institute of Surgical Research in the aeromedical transfer of literally thousands of burn patients—in which experience we have found that a large percentage of the patients require management of catheter problems, alterations in ventilatory management, or alteration of fluid therapy by the surgeons of our burn teams, either prior to or during flight.

Since speed of transfer doesn't seem to be a significant factor in the outcome of these patients, but prompt institution of trauma center-guided therapy does, do the authors feel that education of and improved communication with their referral sources would improve the level of care given to the ground transport patients?

We insist on physician-to-physician communication before accepting burn patients for transfer, and I wonder whether the authors feel that this could be done in their system of trauma care and whether it would make a difference.

There are several questions the answers to which will assist us in evaluating the authors' conclusions. Since the outcome of a population of trauma patients is strongly influenced by central nervous system injury, it is of concern that a greater percentage of the ground-transported patients, as indicated in both Tables I and II, had CNS involvement, and one wonders what role that played in the observed outcome.

It is puzzling that, with the higher incidence of CNS injury, the ground-transported patients had a higher Glasgow trauma score, and I ask the authors how they might explain that apparent paradox. Since the trauma score may change with time, I also ask the authors whether the postinjury time of trauma score determination was comparable in the two groups of patients.

The authors state that the charges for air medical transfer represented only 15% of costs and that the remaining 85% were subsidized by other inpatient revenues as a most laudable institutional commitment to trauma care. That is, as the authors suggest in their manuscript, a strong argument for improved triage, since 74% of the air-transported patients had trauma scores above 9 or below 4, and outcome in those patients was not influenced by the means of patient transport. Do the authors have a plan to improve triage accuracy within their system?

I compliment the authors on this important study that redirects misplaced emphasis from speed of patient movement by air transport, and demonstrates the advantage of transporting an extension of the emergency center to the injured patient.

As a final question, I ask the authors if they plan to take the next step and include a surgeon in their trauma flight teams?

DR. GEORGE F. SHELDON (Chapel Hill, North Carolina): I enjoyed the paper very much. As we at the University of North Carolina are 8 miles away and back each other up when helicopters develop their inevitable mechanical problems, we see many of the same problems. Dr. Moylan's paper, among other things, proves the value of excellent prehospital control of transport. It documents the value of the skilled flight attendants and nurses that work with Drs. Moylan, Georgiade, and the Duke team.

With only four Level I trauma centers in the state and because most of our hospitals are small and lack the resources to care for the multiply injured patient, the helicopter is needed in North Carolina. Moreover, Susan Baker recently reported that for comparable levels of injury severity score (ISS), mortality rates in rural areas are four times that of patients having the same injury in urban areas.

I would add an interpretation of the data presented by Dr. Moylan. I think the greater time spent in the hospital prior to transport may represent local evaluation and resuscitation time. The problem everyone is addressing is availing the resources of the Level I center to patients within the golden hour.

As someone who is not very enthusiastic about MAST trousers, I would also ask if you have data or strong conviction that MAST trousers have improved outcome. I recognize this is a debatable area.

The last question is philosophical (Slide). Dr. Warren Cole of this Association pointed out a problem that we are going to see more of as we develop sophisticated Level I centers. He pointed out (in 1957) that the mechanisms for obtaining training in trauma are so inadequate that care should be given to development of training programs in the field. We now train 2,750 surgeons a year; 400 remain in general surgery. Level I requirements for directors are that there be general surgeons to direct the trauma teams as Level I leaders. I think one of the exceptions is Dr. Georgiade at Duke, who is a plastic surgeon deeply involved in the trauma transport program.

My last question is, where will we get people to run trauma teams as you have done so well at Duke?

DR. C. WILLIAM SCHWAB (Philadelphia, Pennsylvania): Dr. Haynes and Jones: I rise to compliment the authors on their observations. It is always nice to hear a paper that supports your prejudice. In 1983 we reported a similar study. Unfortunately, we did not have data to look at outcome, but we did notice that helicopters were bringing in sicker people (higher ISS, lower TS) and that these people were surviving. I have several questions for Dr. Moylan.

I take some issue with your methodology and, in particular, your heavy reliance on trauma score as the only barometer of the severity of injury. Why didn't you use the Injury Severity Score and, specifically, why not include a breakdown of the Abbreviated Injury Score (AIS)? Our own observations have been that head injury, in and of itself, is not only the most lethal, but the most costly single injury seen at a trauma center. However, other combinations, particularly head and chest injury, carry a very high mortality and a high cost. It may have been important to see if anatomic injury correlated with cost.

(Slide) As to the economic issues Dr. Moylan introduced, I believe this paper offers too simple a view and, in fact, may be misleading. First of all, this slide shows the data from a 1-year study we performed in southern New Jersey at a state-designated Level I trauma center. It represents an experience with 523 patients (80% blunt MVA's) admitted to a single hospital that receives its entire reimbursement from a state-regulated prospective payment system (DRG). This system is similar to the reimbursement system used for federal medicare. Additionally, during the time that these 523 patients were admitted, prehospital anatomical triage guidelines were practiced by the EMS providers so that true regionalization was taking place. In essence, high severity patients were concentrated in this hospital. As you can see, the average stay was approximately 15 days, the mean ISS was 15.6, and when we compared cost and state reimbursement, we *lost* \$3562 on *every* admission. Also note from the slide, as severity of injury increased (higher ISS), so did hospital cost and also the economic loss!

Secondly, if we break out the outliers, as seen in this slide (outliers being defined as those patients that exceeded the normal length of stay for any given DRG), we lost an average of \$7200, twice that of all cases. Outliers tend to be the most severely injured patients, and, in our outlier group, 60% had an Injury Severity Score above 16. These patients tend to be those type of patients that helicopters, like those in Chapel Hill or Duke, bring into the medical center. Also notice the increasing loss per case, again correlating with higher ISS or severity of injury.

I realize that New Jersey is probably 5 to 6 years ahead of the United States with regards to its experience with prospective payment, and North Carolina obviously does not have the problem just yet. However, Dr. Moylan, I wonder whether if you were to scrutinize your financial data, would you find among your Medicare/DRG population an experience similar to ours in New Jersey? As prospective payment is adopted by the third party payers to solve the medical inflation problem, and as the elderly population continues to grow, this small hidden problem may come to dominate your fiscal officer's headaches. Our experience with prospective fixed reimbursement has led us to conclude that this is the greatest problem and challenge for future funding of any trauma center, helicopter or not.

Once again, I enjoyed the paper; and I thank the association for the privilege of discussing it.

DR. FRANCIS T. THOMAS (Greenville, North Carolina): Dr. Moylan has presented a very nice study of a patient group with trauma scores between 5 and 10. I think this is one of the first and best communications from a nonurban setting documenting this in a well studied group of patients.

Since Baron Larrey first introduced the ambulance, we have seen a movement towards a rapid transport system for patients, with the helicopter offering our latest option in this area. The "Golden Hour" concept is truly put to the test in a rural environment. The helicopter proliferation, as many of you know, has been exponential. This has resulted in the widespread distribution of hospital helicopters. In many states, the activity has been so intense that it has been referred to as the "helicopter wars."

I think that Dr. Moylan has shown us that there is, indeed, a strong medical rationale for the helicopter, not so much to decrease the time of transport of the patient, but rather to permit the more wide-spread use of field personnel that are highly trained and have the capability of a Level I Trauma Center. This expertise is brought to the patient at the accident site and continued on the way to the hospital.

I have two questions for Dr. Moylan. Joe, what do you feel are the appropriate and optimal distributions for this type of service and for Level I trauma centers? Do we need any more specialization? Does there need to be any redistribution of the type of resources and facilities available in any of them?

Secondly, what can we do to prevent the tragic helicopter crashes that we hear of all too often? Having been through one of these experiences at our hospital, I can tell you that the effect on the entire hospital staff is truly extraordinary.

DR. ARTHUR J. DONOVAN (Los Angeles, California): I had not intended to discuss this paper, but the question of funding for trauma care has been raised, and I rise to comment in that regard.

In Los Angeles, an area of 7 million people, a trauma system was established, with Level I trauma centers appropriately spaced. Within the last 2 years, six private hospitals have withdrawn from the system because of inadequate funding for patients without any or with inadequate payment capability. This has put an enormous strain on the remaining hospitals. Neither the state, the County, nor the Federal Government has been willing to address the issue of funding for the care of the trauma patient. This issue needs to be addressed.

DR. JOSEPH A. MOYLAN (Closing discussion): I appreciate all the discussants and their contributions to what we think is an important issue.

Dr. Donovan, we agree with you that funding is a major problem. The majority of our patients, as you observed, were motor vehicular trauma. In our state there is some mandatory collision insurance that covers some of these hospital charges.

Dr. Thomas, distribution of trauma centers is a sociopolitical problem that is very difficult to deal with. I am not sure I have an answer that I can present in the brief time we have here today.

Dr. Schwab, because we are focusing on the physiologic phase of their care during the first few hours, we chose to use the trauma score, although we do have the ISS and the AIS on all our patients. ISS and AIS are retrospective, based on anatomic injuries and are probably more important for comparing long-term hospitalization and finances. In distinction to New Jersey and the data that you reported, the inpatient revenues that covered our helicopter operation came from the trauma unit itself.

We experienced a budgetary surplus last year in our trauma unit, since most of our patients are not penetrating trauma and do have third party coverage.

Dr. Sheldon, we appreciate the comments you made about MAST trousers. We are also concerned about their hemodynamic value. I think that in many instances, the MAST trousers are used to stabilize long bone fractures. I am not sure what their hemodynamic value is.

In terms of time in the emergency room, we felt that in our series most doctors call us earlier for the helicopter, rather than later when they are transporting them by ground.

How trauma surgeons are going to be trained in the future will be determined by the committment made by general surgical training programs, and we all have to address that issue.

Dr. Pruitt, we do have a medical control officer who accepts every flight as does the Army Burn Center in San Antonio. We do find, however, that there is a gap between what you direct the referring doctor to carry out before you transport and what he actually does.

Again, the difference in the number of head injuries and the Glasgow is an important point, as you have observed. There were a few more head injuries in the ground group. However, they were less severe, as reflected by the higher Glasgow score.

We are not going to send a trauma surgeon on our flights. Basically, the interventions we have found important included intubation, the use of blood, and the placement of chest tubes. Our personnel are skilled in those things, and we do not feel we have the resources to expend a surgeon to do that.

The Capacity of Serum to Support Neutrophil Phagocytosis Is a Vital Host Defense Mechanism in Severely Injured Patients

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The opsonic capacity of patient serum was studied in 43 trauma patients of whom 13 recovered uneventfully, 21 developed major infection, and nine died, mostly of infection. Blood samples were taken within 24 hours of injury. Fifteen patients were studied serially of whom 14 developed severe infection and/or died. Opsonic capacity was determined by flow cytometry and measured as the ability of normal neutrophils to phagocytose killed bacteria previously incubated with patient serum. The most dilute sera reflected changes for better and worse most clearly. On initial assessment, those who died of sepsis showed a 61% mean fluorescent intensity (MFI), which was significantly lower than the 99% MFI for those who survived infection ($p < 0.01$) and the 78% MFI of those who developed no infection ($p < 0.05$). Serial samples demonstrated a super serum response in four of seven patients surviving major sepsis but in none of the seven who died of infection.

TRAUMA IS A MAJOR CAUSE of both mortality and morbidity in this country.[1] Approximately one-half of trauma-related deaths occur at the scene of injury, and thus, accident prevention is the primary hope for reduction of these deaths. Of the patients who arrive at the hospital alive, one-half of those destined to die do so within the first few hours, usually from uncontrollable hemorrhage or closed head injury. The majority of the remainder of deaths and most major morbidity rates in those patients who survive initial resuscitation are due to infection.[2] Despite great improvements in surgical treatment, perioperative support, and broader antimicrobial usage,[3] infection remains a serious problem and plays a particularly decisive role in the trauma victim. Detailed analysis of a variety of host defense mechanisms has been performed as effective means to stimulate the depressed immune system in these patients continue to be sought.[4]

In an effort to determine which aspects of the immune system are most directly affected after trauma, a long-range study of a variety of parameters of both cellular and humoral immunity from severely injured patients was undertaken.[5] Of all parameters tested, the ability of peripheral blood monocytes to express HLA-DR and the ability of patient serum to support phagocytosis of bacteria by normal neutrophils were found to be of dominant importance. For convenience, the phrase, serum opsonic capacity, will be used in place of capacity of serum to support phagocytosis by normal neutrophils. Such severely injured patients were studied to determine if certain patterns of serum opsonizing capacity could be identified and to what extent these correlated with eventual clinical outcome.

It is well recognized that the ability of neutrophils to phagocytose bacteria is reduced following trauma.[6,7] However, major intrinsic polymorphonuclear leukocyte dysfunction in these patients has not been consistently shown. The impaired capacity of neutrophil phagocytosis may therefore be due to serum factors rather than instrinsic cellular defects.[8,9] A recent study found no difference between phagocytic indices of neutrophils from infected and nonseptic trauma patients,[10] and others have shown complement-dependent deactivation and damage of circulating neutrophils as well.[11] This paper reports a continuing study of the ability of sera from severely injured patients to support opsonization of bacteria for phagocytosis by normal donor neutrophils. The effects of both complement-dependent and

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complement-independent serum opsonic capacity in badly hurt patients are further examined.

Materials and Methods

Patient Population

Forty-three consecutive patients admitted under the care of the emergency surgical services at the Humana Hospital-University of Louisville, KY, were studied. Only patients who had sustained major trauma resulting in an injury severity score (ISS) of at least 20 were accepted. To allow more meaningful comparisons between equivalent injuries in patients of different ages, the concept of expressing the ISS as percentage of the LD_{50} for age was used as originally described by Bull.[12] Using a probit fit analysis of burn mortality rates, Bull developed LD_{50} values for three separate age ranges. Individual percentages of LD_{50} values were calculated by dividing the ISS of each patient by the appropriate LD_{50} for age and expressed as a percentage (%LD_{50}). Patients with a previous medical history of myocardial infarction, organ failure, neoplastic disease, or current immunosuppressive therapy (steroids or cytotoxic drugs) were excluded. Patients transferred from other centers after initial stabilization were accepted; however, those transferred after prolonged care were excluded. Informed consent was obtained from the patient or relatives in all cases.

Patient outcome could be divided into the following three groups: (1) a good outcome group who did not develop major sepsis (N = 13); (2) a major sepsis group (N = 21); and (3) a group who died (N = 9). Seven of the nine patients who died did so in a septic state and usually with multiple organ failure. The other two died within 4 days of admission from progressive hypoxia. Major sepsis was described as every instance of bacteremia, all of which were associated with definable clinical problems, major wound infection, intra-abdominal or other serous cavity abscess, and any situation in which reoperation for suspected infection was undertaken.

Contamination present at the time of admission or surgery was graded as follows: massive soft-tissue contamination or large bowel spillage (2+), minor soft-tissue, intrathoracic, or abdominal contamination (1+), or no contamination. Venous blood samples were obtained from each patient within 24 hours of admission. There was insufficient serum from one patient who died to carry out the heat inactivated analysis. In addition, 15 patients had serial serum samples taken approximately every 3 days throughout their hospital stay. These patients were selected on the basis of a high likelihood of developing severe infection from their initial clinical presentation. Another patient who developed necrotizing mycofasciitis and died with chronic sepsis was also serially studied.

Serum Opsonic Capacity

Individual serum samples were tested for their ability to opsonize *Staphylococcus aureus* for phagocytosis by neutrophils obtained from a normal volunteer. Formalin-killed bacteria were stained with a fluorescent dye (Texas red). The stained bacteria were incubated for 30 minutes at 37 C with dilutions of test serum or control pooled human serum. A paired aliquot of serum was heat inactivated at 56 C for 45 minutes to determine whether the opsonic capability of the serum was complement-dependent.

The bacteria were washed and incubated for 30 minutes at 37 C with the normal leukocytes. Each sample was then washed and fixed in paraformaldehyde. Phagocytosed bacteria were detected using a cytofluorograph II flow cytometer (Ortho Diagnostics, Westwood, MA).

Data were recorded as the mean fluorescent intensity emitted from neutrophils, which ingested one or more bacteria. Mean fluorescent intensity was expressed as a percentage of control values obtained by using pooled human serum (%MFI). Two thousand neutrophils were analyzed in each sample.

Statistical Analysis

The Student's t-test was used to determine differences between patient outcome groups. Wilcoxon ranking sum test was used to determine differences in the degrees of contamination on admission between the groups with uneventful recovery, major infection, and those who died. Differences were considered significant at $p < 0.05$.

Results

The mean ISS of the patients was 35.7, and the mean %LD_{50} was 102. The median contamination of the uneventful recovery group was 0, which was significantly less than both the septic group (median: 1) and the dead group (median: 2). The respective means were 0.38, 1.24, and 1.44 of the three clinical outcome groups. The differences between the septic and dead groups were not significant. Initial total serum %MFI values are shown in Table 1. The group who ultimately died had initial %MFI values significantly less than both the septic and good outcome groups at serum dilutions of 0.5 and 5.0%. Although the differences at 1.0 and 10.0% serum dilutions did not reach statistical significance, the trend was similar. This reduced capacity for opsonization in patients who ultimately died was even more clearly seen

TABLE 1. *Opsonic Capacity Expressed as Percent Mean Fluorescence Intensity*

Serum Concentration (%)	Nonseptic (N = 13)	Septic (N = 21)	Dead (N = 9)
0.5	78.0 ± 5.0*	99.0 ± 9.0*	61.0 ± 5.7
1.0	75.5 ± 7.4	89.8 ± 6.4	66.0 ± 6.8
5.0	82.3 ± 5.3*	90.8 ± 6.1*	56.7 ± 7.7
10.0	80.7 ± 7.1	85.1 ± 5.9	68.0 ± 10.5

* Significantly different from dead group ($p < 0.05$).

TABLE 2. *Complement-independent Opsonization (%MFI Heat Inactivated Serum)*

Serum Concentration (%)	Nonseptic (N = 13)	Septic (N = 21)	Dead (N = 8)
0.5	97.8 ± 2.7*	99.0 ± 7.4*	58.1 ± 11.9
1.0	90.0 ± 5.4*	87.0 ± 5.7*	53.1 ± 7.4
5.0	96.0 ± 7.5*	86.4 ± 4.9*	54.9 ± 19.4
10.0	110.0 ± 7.7*	97.3 ± 7.1*	66.1 ± 8.3

* Significantly different from dead group ($p < 0.05$).

in heat inactivated serum (Table 2). The group of patients who died had heat inactivated %MFI values significantly less than both the septic and good outcome groups at all serum dilutions analyzed.

The most dilute sera reflected the most widely varying opsonic capacity changes. Septic patients had greater total %MFI values than nonseptic patients (Table 1) but did not display greater heat inactivated %MFI values except in the dilute serum (0.5%, Table 2). The difference in serum opsonic capacity between septic and nonseptic patients was determined by subtracting the mean %MFI value of nonseptic patients from the mean %MFI value of septic patients at each serum dilution (Fig. 1). This was also calculated for the septic and dead patients. The differences in total %MFI were seen most clearly at the lowest dilutions. This curious observation that the most dilute sera consistently reflected opsonic capacity changes most clearly was also seen in the serially followed patients. Furthermore, it reflected both beneficial and detrimental changes. Two examples emphasize this. A 27-year-old man sustained a shotgun wound to the abdomen and bony pelvis. He developed intra-abdominal sepsis and osteomyelitis but survived these infections. The 0.5% serum dilution consistently reflected the highest %MFI detected throughout his illness (Fig. 2). At the opposite end of the spectrum was a 62-year-old woman who sustained severe blunt chest trauma and multiple extremity fractures. She developed adult respiratory distress syndrome and chronic refractory pneumonia from which she ultimately died 157 days after injury. Her 0.5% serum dilution was consistently the lowest %MFI that was detected throughout her hospital course (Fig. 3).

The patient data, outcome, and opsonic capacity changes are summarized in Table 3. The observation that patients who survived sepsis tended to have elevated %MFI values led to characterization of a super serum response, which occurred when %MFI values exceeded 150% of normal pooled human serum. An example is shown in Figure 2. This super serum response

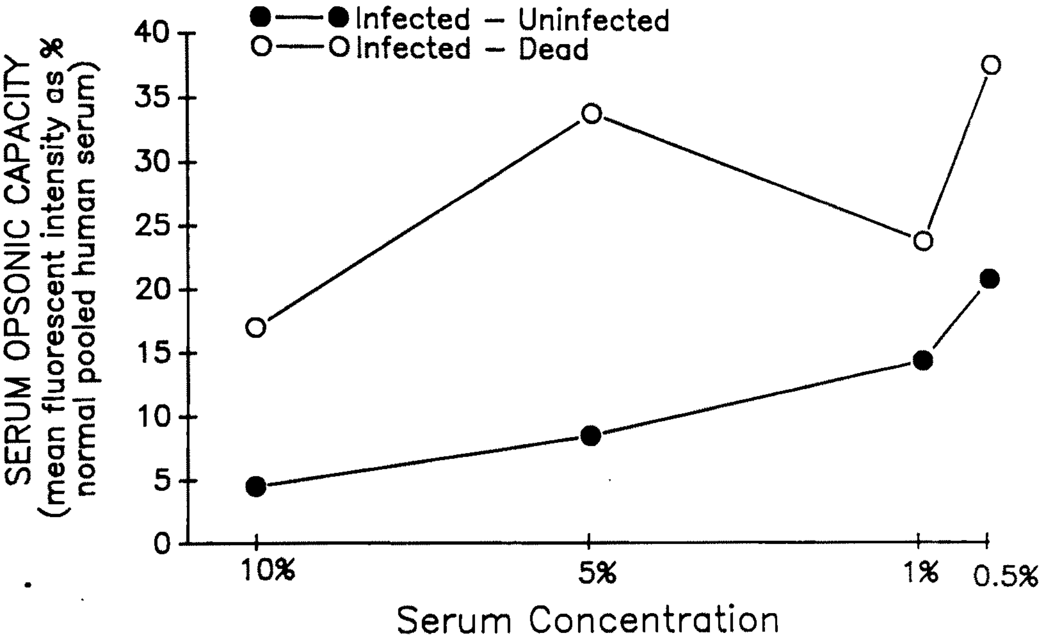

FIG. 1. The relationship between serum concentration and the differences in opsonic capacity (%MFI) of both those who developed sepsis and those who died, and those with sepsis and those who recovered uneventfully.

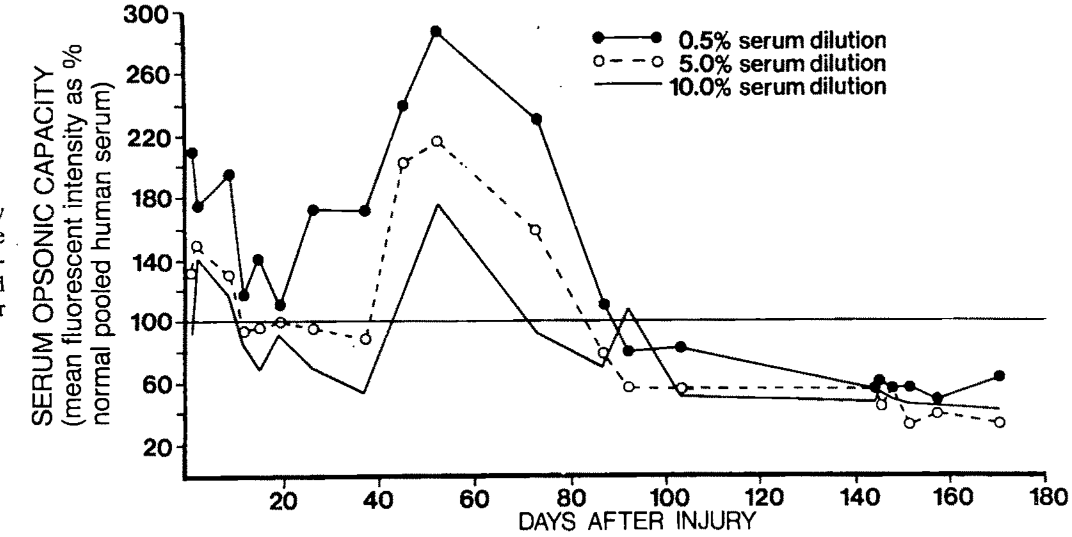

FIG. 2. Opsonic capacity (%MFI) at three separate serum dilutions as a function of time in a 27-year-old man who survived major infection.

occurred in four of seven patients surviving major sepsis and in none of the seven who died of infection.

Heating serum at 56 C for 45 minutes eliminates complement-dependent phagocytosis and also serves as an internal control for the process. Both the patient with necrotizing fasciitis and the one trauma patient who died from chronic infection demonstrated similar opsonic capacity changes, which were not seen in any patients who survived sepsis. These changes included a progressive depletion of total %MFI values together with unchanged heat inactivated %MFI (Fig. 4), indicating depletion of complement-dependent opsonic components, a phenomenon previously referred to as "consumptive opsoninopathy."[13] Note also the relative stability and/or protection of intrinsic complement-independent opsonic activity.

Discussion

Reduction in both serum opsonic capacity and opsonin levels has been shown to occur immediately following major trauma, but only variable correlation with subsequent infection has been documented.[14-17] Replacement of depleted opsonic fibronectin has been shown to restore serum opsonic capacity utilizing radioisotope techniques,[18] but correlation with clinical outcome has not been done. These results demonstrate a significant correlation between initial serum opsonic ca-

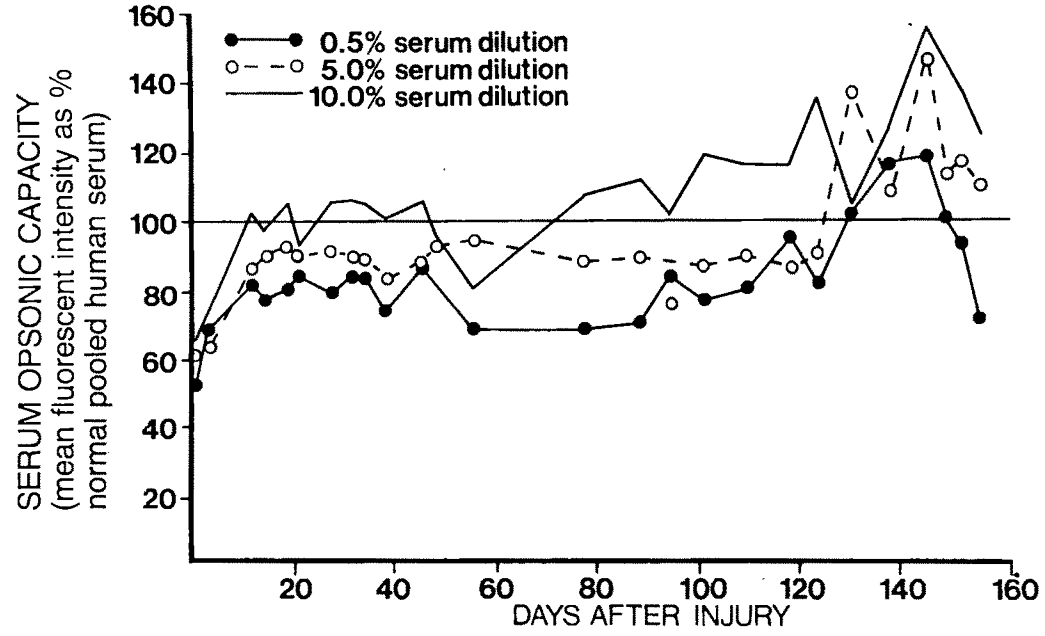

FIG. 3. Opsonic capacity (%MFI) at three separate serum dilutions as a function of time in the 62-year-old woman who died from infection.

TABLE 3. *Analysis of Serially Sampled Patients*

Mode of Injury	ISS	%LD$_{50}$*	Clinical Outcome	Opsonic Capability Changes
Crush	25	60	Major sepsis	—
SGW	29	73	Major sepsis	—
GSW	34	85	Uneventful recovery	—
MVA	34	85	Major sepsis	Super serum
Burn	25	86	Major sepsis	Super serum
SGW	35	88	Major sepsis	Super serum
SGW	38	95	Major sepsis	Super serum
Fall	38	95	Chronic major sepsis	Consumptive opsoninopathy
Fall	43	108	Septic death	—
Burn	50	125	Septic death	—
GSW	50	125	Nonseptic death	—
Burn	25	125	Septic death	—
Burn	41	141	Septic death	—
MVA	41	141	Septic death	—
MVA	50	250	Nonseptic death	—

* Bull.[12]
GSW = gunshot wound.
SGW = shotgun wound.
MVA = motor vehicle accident.

pacity and ultimate death associated with infection for both total and heat inactivated serum. Patients who ultimately died had significant reduction of both complement-dependent and noncomplement-dependent opsonic capacity. Furthermore, markedly reduced opsonic capacity within 24 hours of injury was predictive of death at a time well before the onset of clinical sepsis. Interestingly, a recent report,[19] using an entirely different method to assay neutrophil function, also concluded that serum factors are substantially responsible for some diminished neutrophil activity following general anesthesia and elective operation.

In patients who made uneventful recoveries, the total serum opsonic capacity was reduced, but the complement-independent opsonic capacity remained normal. It appears then that major trauma primarily affects complement-dependent opsonic capacity. In contrast, patients who developed major sepsis but survived had both normal total and heat inactivated capacity. Thus, the ability to restore subnormal complement-dependent serum opsonic capacity to normal appears to be a beneficial host defense mechanism in those who develop infection.

The ability to increase serum opsonic capacity was beneficial in serially studied patients. Twelve patients developed major infections and five died from such infection. Six of the seven who survived major infection dealt with their infection well initially, and all of these were able to increase their opsonic capacity. Four of them increased the total opsonic capacity to greater than 150% of normal, defined as super serum. One patient (Fig. 2) produced a %MFI as high as 300% of normal during his infection before he recovered. In contrast, inability to increase opsonic capacity in the face of infection was detrimental. No patient who died increased his opsonic capacity to the super serum range, and most actually had a downward trend. One patient who developed a consumptive opsoninopathy (Fig. 4) had severe reduction in complement-dependent opsonic capacity but normal heat inactivated opsonic capacity. This phenomenon did not occur in any other of our trauma patients. Such changes were seen, however, in another

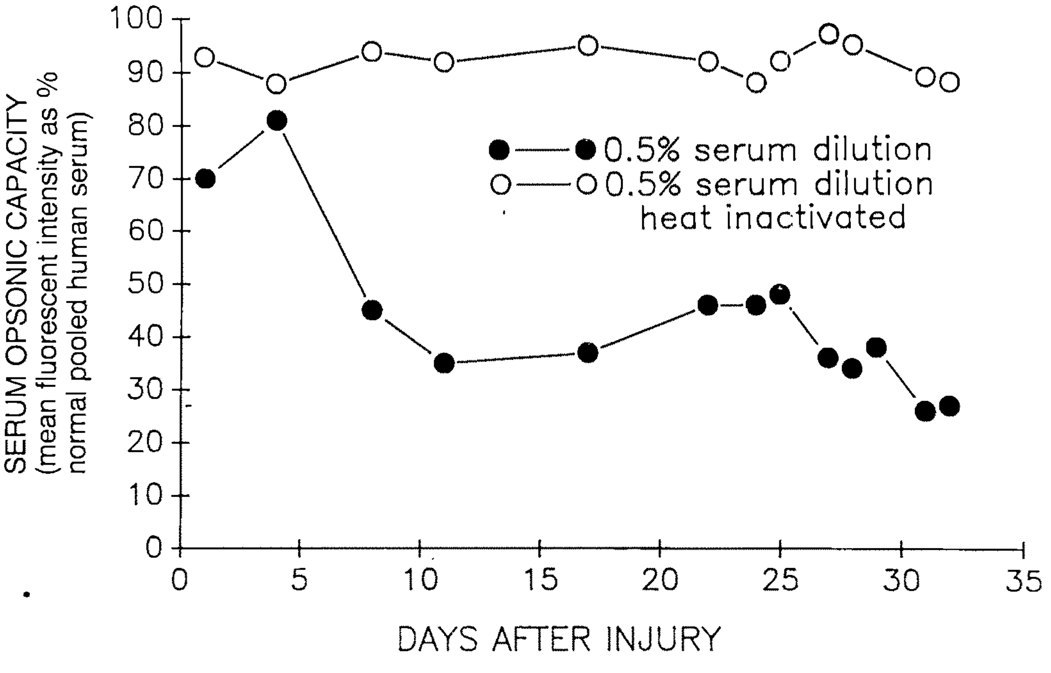

FIG. 4. Mean fluorescent intensity of both total and heat inactivated serum as a function of time in a patient with consumptive opsoninopathy. The total opsonic capacity is expressed as a percentage of normal non-heat inactivated pooled human serum. In contrast, heat inactivated serum opsonic capacity is expressed as a percentage of heat inactivated normal pooled human serum.

patient with necrotizing fasciitis who eventually died of his infection.

The most dilute serum most clearly reflected opsonic capacity changes whether beneficial or detrimental. Considering day 1 samples, the difference in opsonic capacity between surviving patients who developed sepsis and those who died as well as those with uneventful recoveries was most pronounced at the lowest dilutions, as seen in Figure 1. Dilution of certain inhibitors of opsonization might explain this phenomenon in certain situations, such as the patient represented in Figure 2. Such inhibitors have been previously identified[20,21] and are common manifestations of competitive inhibition at receptor sites. Levels of suppressor active peptide have been found to be significantly elevated in burn patients who died compared to those who survived.[22] The importance of dilution was seen not only at the initial measurements but also serially; however, it is not clear why the patient who eventually died (Figure 3) would have the lowest values represented by the most dilution. The trend of the most dilute sample reflecting the greatest difference held up for both total and complement independent opsonic capacity.

Clearly, severity of injury, age, and degree of bacterial contamination at the time of injury are major factors in determining clinical outcome of the trauma patient.[23] In this study, the importance of bacterial contamination as a determinant of outcome and opsonic capacity changes was observed. Patients destined to make uneventful recoveries, develop major sepsis, and die had median degrees of contamination of 0, 1, and 2, respectively. The higher initial levels of total opsonic capacity seen in septic compared to nonseptic patients (Table 1) may be related to greater bacterial challenge. Interestingly, serum opsonic capacity changes bore no relationship to monocyte HLA-DR expression, which independently distinguished between different clinical outcomes.[5] Similar to the prediction of septic death by the first determination of serum opsonic capacity, the first monocyte HLA-DR result also was predictive of death and associated infection. A further similarity between serum opsonic capacity and monocyte HLA-DR expression was that in the serially studied patients, two distinct patterns were found in those patients who died of infection and those who recovered from their infection. The mutual influence of these valuable predictors cannot be differentiated at this point. Assessment of the immune capability of the host must be taken into account, and reduced ability of patient serum to support phagocytosis is extremely predictive of fatal outcome. Furthermore, the ability to markedly increase opsonic capacity in the face of infection appears to demonstrate an intrinsic beneficial aspect of host defense against infection in these patients.

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DISCUSSION

DR. EDWIN A. DEITCH (Shreveport, Louisiana): I would like to begin by congratulating Dr. Polk on an excellent presentation and also thanking him for getting the manuscript to me in time to sort through the data.

As we have seen, this presentation does deal with a complicated subject.

We know that the initial host defense against invading bacteria is, as Dr. Polk has said, the nonspecific host defense system. This is comprised primarily of the reticuloendothelial system, neutrophils, and humoral factors, such as complement. We also know that for neutrophils to function efficiently, the bacteria need to be buttered with humoral opsonins.

What Dr. Polk has shown us today is that after major injury, the opsonic capacity, or the ability of the serum of these patients to support the normal ingestion of bacteria, is reduced.

He has further shown that this reduction in opsonic activity is of predictive importance.

For a prognostic factor to be important, it needs to identify a patient at risk, but for a prognostic factor to be clinically important, it needs to have a causal relationship to something that can be altered.

The first question I have for Dr. Polk and his colleagues is: What is the relationship between the defect in opsonic activity and the development of infection?

The reason I ask this is that we have performed similar studies on burn patients. (Slide) If we collect serum from these burn patients within 24 hours of injury and measure C3, and plot its value against the magnitude of the injury, we find a nice inverse relationship, with patients having the biggest burns having also the biggest decrease in serum complement levels.

This decrease in C3 levels appears to be due to intravascular dilution or extravasation, since C3 activation products are not increased. Dr. Polk, is there any relationship between the magnitude of the injury (that is, injury severity score), and the level of opsonic activity of your patients upon admission?

Also, were there any relationships or differences between the injury severity scores of the three groups you identified: the patients who never became septic, those who became septic and did well, and those who died?

My laboratory has measured the opsonic activity of blister fluid in a neutrophil-mediated bactericidal assay. That is, we tested the ability of this fluid to support normal neutrophils in killing bacteria, and found that blister fluid would not support normal bactericidal activity, whereas when we added normal serum back to the blister fluid, bactericidal activity returned to normal.

We have done some repletion studies in which we added back either heated inactivated serum, which did not restore activity, purified IgG, which did not restore activity, or normal serum which did restore activity. So our working concept is that the decreased opsonic activity of blister fluid is due to a consumptive opsonopathy rather than to the presence of inhibitors. Although I think Dr. Polk's point that one may be diluting out the inhibitor is true, one may also be diluting out active components. Thus, an alternative explanation is that the serum does not have a defect, because there are adequate levels of complement components left, and only after further diluting out the serum is there a deficiency of factors that becomes apparent.

My second question, then, is: What is the mechanism for the decrease in opsonic activity? Have you done any studies that try to nail down whether this impaired opsonic activity is due to an inhibitor, or to determine whether this activity is due to a lack of normal factors?

My last question deals with the utility and possible interpretation of your findings. Do you believe that this defect is clinically important *in vivo,* since the cells circulate in 100% serum, not in 0.5% serum? Do you believe this defect is causally related to the development of infection, or do you believe that it is currently used primarily as a screening test to identify patients who are at increased risk of developing infections?

In conclusion, I would like to compliment Dr. Polk and his coworkers on a very interesting study, the beginning of a "story" for which I am sure more "chapters" will be written, and I hope that after this story has been told, we will have a better handle on why patients become immunosuppressed, and what we can do to reverse that immune suppression.

DR. ANDREW M. MUNSTER (Baltimore, Maryland): It is always a privilege to hear one of Dr. Polk's papers, and this one is as scintillating as his previous ones have been on the subject.

I have three questions. One relates to Dr. Deitch's earlier discussion. Some of the opsonic factors in serum are well known—IGG, for example—and these would be relatively easy to measure. Did he, in fact, initially measured some of these fairly simple things?

I am very intrigued by the fact that *Staphylococcus aereus* was the only test organism, and yet "septic patients" following trauma die mostly of gram negative sepsis, and the mechanism of opsonization is actually quite different, or *may be* different, for the two types of organisms.

So my second question is: What were the causative organisms of sepsis and death in this group of patients?

And my final question is perhaps a little puckish. We know that Dr. Polk has been playing with immune restorers, MDP being one. Have you tried to mix a little MDP into the pot and see if that improves the fate of the neutrophils?

DR. WILLIAM G. CHEADLE (Closing Discussion): I will respond first to Dr. Deitch. The clinical outcome groups were comparative with regard to injury severity score (ISS). In other words, there was no significant difference in the ISS of the good, the septic, and the dead groups. However, if one corrects the ISS for age, which gives the %D50, the dead group does have a significantly greater %LD50 score than the two groups of surviving patients, and this means the dead group constitutes an older age group.

We have not attempted to correct the defect in opsonization found in these patients by adding either normal serum, fresh frozen plasma, or other opsonic components. We have begun to attempt restoration of HLA-DR expression on monocytes, however, and if one adds compounds such as MDP, lipopolysaccharide, or interferon-gamma, these will produce an increase of depressed DR expression back to normal.

We have run the phagocytic assay at several different dilutions, all well below serum concentration, because actual differences become detectable at these dilutions. It may well be that dilution of certain inhibitors of opsonization is necessary for bringing out these changes. I think the assay has great potential, not only as a screening test to identify those patients at high risk of infection and death, but also in the evaluation of immune adjuvants in experimental models of infection.

Dr. Munster, we have measured serum IgA, IgG, and IgM serially, in these patients, and there is an initial reduction of serum IgG and IgM, with the exception of IgM in burn patients. This reduction of serum immunoglobulins may be partially responsible for the low values of certain groups in both the complement dependent and independent phagocytic assays, but does not explain the near-normal values seen in the heat inactivated assays of the surviving groups. We used the Collin's strain of Staph aureus, which is rare and to which there should not be preformed antibodies that would artifically increase serum opsonic capacity in the assay.

The scope of this particular research has been to identify in the severely injured patients immune parameters that, when measured early in the hospital course before the onset of sepsis, correlate with infection and death. In addition to age and degree of contamination, monocyte HLA-DR expression and serum opsonic capacity both correlate highly with clinical outcome. Correction of these defects with immunomodulators may prove beneficial to clinical outcome.

The Role of Feces, Necrotic Tissue, and Various Blocking Agents in the Prevention of Adhesions

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Ischemic tissue and intraperitoneal bacteria have been ascribed an etiologic role in the production of intra-abdominal adhesions. To further elucidate the role of these stimuli and to evaluate the potential protective effect of various agents, peritonitis was induced in 160 Sprague-Dawley rats. The experiment was stratified into those animals with peritonitis plus necrotic tissue, solid feces, both, or neither. The agents tested were a nonsteroidal anti-inflammatory (ibuprofen), free radical scavenger (SOD), and an anticoagulant (heparin). Death was less likely to occur in animals treated with heparin (3 of 40 *vs.* 12 of 40, $p < 0.01$) or SOD (4 of 40 *vs.* 12 of 40, $p < 0.05$). Ibuprofen did not increase survival in this model. Heparin protected against adhesions in animals with an ischemic ileum of limb and without solid feces. In animals with a nonischemic isolated segment of ileum and solid feces, adhesion formation was increased in both the ibuprofen and the heparin treatment groups ($p < 0.05$).

SINCE THE EARLIEST TIMES surgeons have been aware that celiotomy has been associated with the production of adhesions. Although the etiology of this exhuberant internal overhealing has remained unclear, a diverse list of treatments has been proposed to decrease the incidence of adhesion formation. These include but are not limited to chyme, fish bladder, carp or ox peritoneum, liquid parafin, olive oil, epinephrine solution, amniotic fluid, amniotic membrane, steroids, nonsteroidal anti-inflammatories, dextran, anticoagulants, saline, povidone iodine, and silicone.

The hypotheses upon which the proposed potential benefits of these different agents were based was often armchair surgical logic.

The importance of abdominal adhesions is obvious to all modern surgeons. Because celiotomy has become commonplace, the most common cause of bowel obstruction has changed from that secondary to hernia, to that secondary to abdominal adhesions.

When the peritoneum has been challenged by a noxious stimulus either in the form of a chemical irritant or a bacterial contamination, it responds with an outpouring of a fibrinogen-rich material that spreads throughout the abdominal cavity. Classic surgical wisdom has proposed that this response can localize infection or speed the body's host defense mechanisms to meet the challenge. Previous studies suggest that this may not be correct.[1-4] In a rodent peritonitis model, minidose heparin has been shown to decrease the incidence of adhesion formation, increase survival, and increase the rate of intra-abdominal fibrinogen clearance.[5]

Ischemia, a bacterial challenge, and the inflammatory response have all been incriminated in the development of adhesions. The present study was undertaken to elucidate the importance of each of these factors on the production of abdominal adhesions and on survival. In addition, various blocking agents have been selected that have a known effect on each of these processes. The effect of each of these blockers are evaluated in a rodent peritonitis model.

Materials and Methods

Peritonitis was induced in 160 male Sprague-Dawley rats weighing 250–300 g. Each rat was fasted for 24 hours and then sedated with ether and anesthesized with pentobarbital sodium given intraperitoneally (dose varying from 7.5 to 10.0 mg). The abdomen was shaved and then prepped with Povidone iodine and sterilily draped. A short midline incision was made and the cecum and terminal ileum were mobilized onto the ab-

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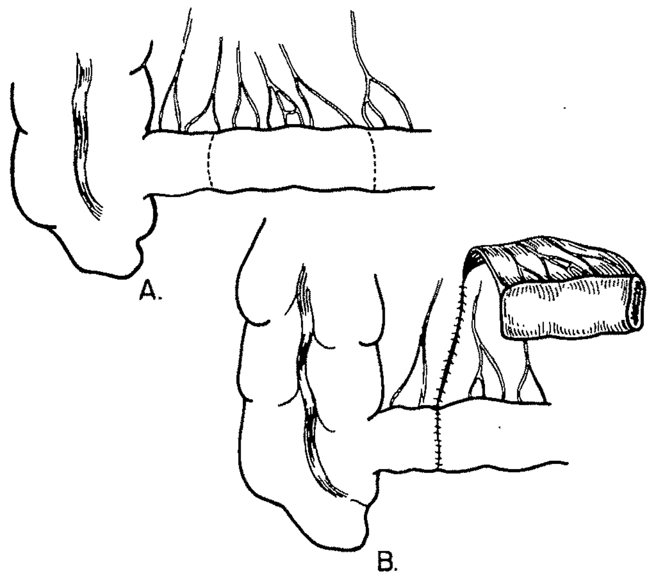

FIGS. 1A and B. The experimental model by which peritonitis was produced.

dominal wall. A 2-cm segment of ileum, 6 cm from the ileocecal junction was isolated on its vascular pedicle (Fig. 1). The intestine was divided at each end of this segment, and intestinal continuity was reestablished by anastomosing the ileum in an end-to-end fashion with 5-0 Vicryl suture. At this point the first variation in the model occurred. In one group, the isolated intestinal segment was left filled with feces, and in the second group, the feces was mechanically removed and the lumen of the segment rinsed with saline. Each group was then divided into two subgroups. In the first subset, the blood supply to the isolated ileum was left intact, and in the second subset, ligation of the vascular pedicle was accomplished with a single 3-0 silk tie. The incision was closed with two layers of absorbable suture. Therefore, the peritonitis challenge consisted of either necrotic intestine (N) plus feces (F) (subset PFN), necrotic intestine without feces (subset PN), viable isolated intestine plus feces (subset PF), or viable isolated intestine without feces (subset P) (Fig. 2). There were 40 animals in each of these divisions. Each division was then divided into four subsets of ten animals each. In each of these divisions, ten animals served as control; ten animals received 15 IU of heparin (H) subcutaneously 1 hour preoperatively and then one injection daily for the subsequent 3 days; ten animals received 3 mg of ibuprofen (IB) intramuscularly 1 hour preoperatively and then intramuscular injections twice daily for the subsequent 3 days; and ten animals received 1800 IU of superoxide dismutase (SOD) intraperitoneally one hour preoperatively and then intraperitoneally once daily for the subsequent 3 days. All animals that died were autopsied, and surviving animals were killed on postoperative day 14. Adhesions were graded by a team of observers on a scale of from Grade 0 (absent) to Grade 3 (matted abdominal contents). A small localized collection of adhesions around the isolated segment of ileum were considered as Grade 1. Mild diffuse involvement with an occasional adhesive band to the abdominal wall was considered Grade 2. Interobserver gradings were extremely constant using this previously established scoring method.

Statistical comparisons were accomplished using the Student's t-test for comparing like groups or chi square analysis for comparison of means of groups.

Results

The survival results are listed in Figure 3. When compared to control, animals treated with H or SOD had a greater chance for survival ($p < 0.01$; $p < 0.05$). Animals

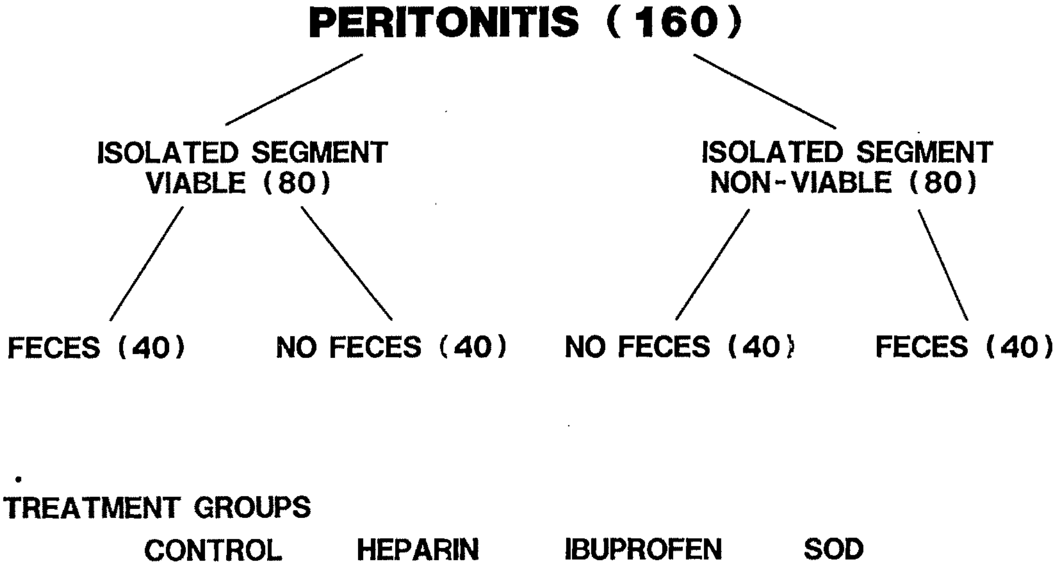

FIG. 2. Flow sheet for the development of the model. In the treatment groups, ten animals acted as control while ten animals were treated with each of the agents listed.

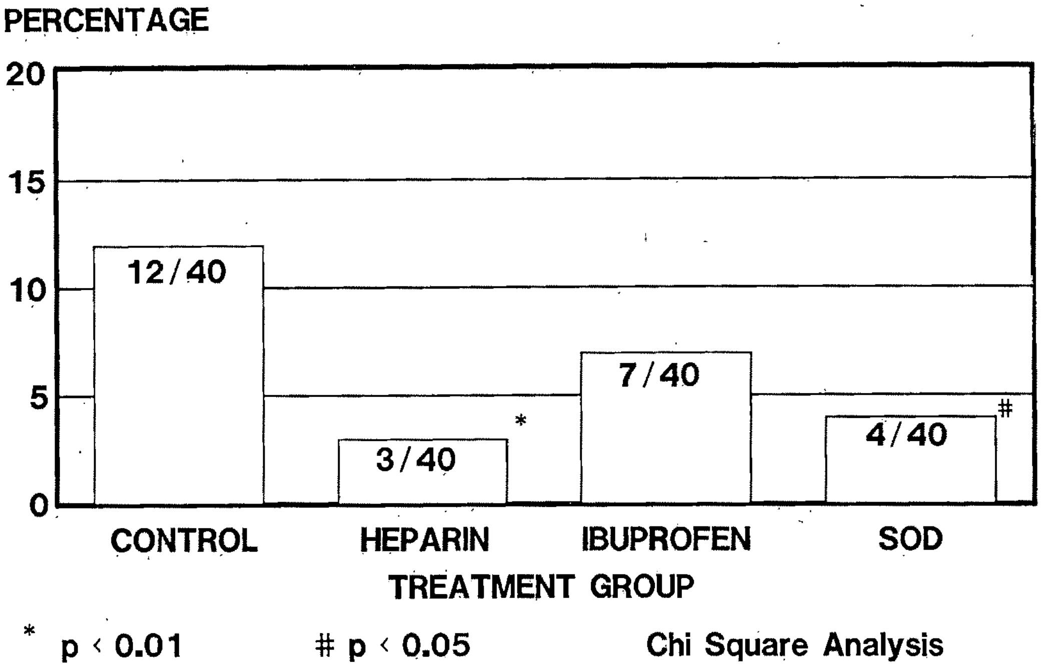

FIG. 3. The death rate for animals by treatment group.

treated with IB did not differ from control. There were no deaths in either the control or treatment groups in animals with peritonitis and a viable ileal segment and no solid feces. The only animals that died in the H treatment groups had a viable ileal loop and solid feces.

When the nontreatment (control) groups were compared, no statistical differences were seen in adhesion formation.

In the animals that had peritonitis alone with a viable segment of ileum and no feces (P) there were no differences in adhesion production between the treatment groups and the control group (Table 1).

In the animals with peritonitis and solid feces but no ligature (PF), there were significantly more adhesions in those treated with IB or H than the control group ($p < 0.05$) (Table 2). The SOD group did not differ from the control group.

In the animals with peritonitis and ligation of the pedicle of the excluded ileum but no solid feces (PN), there was a significant decrease in the amount of adhesions in the animals receiving H ($p < 0.001$) (Table 3). The IB group and SOD group did not differ from the control group.

In the animals with peritonitis, solid feces, and ligation of the pedicle for the ileum (PFN), none of the treatment modalities were effective in decreasing adhesions (Table 4).

Discussion

When the basic premises as to the cause of adhesions were analyzed and challenged experimentally, it became apparent that the causative agents were not as clearly related as previously suggested. The peritoneum's response to a hostile milieu, although multifactorial, seems to descend through a common pathway. For many years surgeons assumed that adhesions were the fibrous scarring that resulted from removing or damaging the peritoneum. Other situations that were thought to predispose to the production of adhesions included rough handling of tissue, evidence of foreign body (talc), active inhibition of fibrinolysis, damage to the peritoneal epithelial lining, healing associated with the exuberant ingrowth of fibroblasts, and the presence of an absorbable foreign body that produced an intense inflammatory response (cat gut and chromic suture).

Von Dembowsky demonstrated in 1888 that defects produced by abrasion or excision in animals were not associated with adhesion formation.[6] These observations were confirmed by Franz in 1902.[7] Similar results were shown by Babcock[8] and Robbins et al.[9] in humans

TABLE 1. *The Degree of Adhesions in Animals with Peritonitis, No Solid Feces, and a Viable Segment of Terminal Ileum.*

Treatment Group	N	Adhesions (mean ± SD)	Significance
Control	10	1.7 ± 0.48	—
Heparin	10	1.8 ± 0.42	NS
Ibuprofen	10	1.8 ± 0.79	NS
SOD	10	1.9 ± 0.32	NS

TABLE 2. *The Degree of Adhesions in Animals with Peritonitis, Solid Feces, and a Viable Segment of Terminal Ileum*

Treatment Group	N	Adhesions (mean ± SD)	Significance
Control	10	1.8 ± 0.63	—
Heparin	10	2.5 ± 0.71	$p < 0.05$
Ibuprofen	10	2.4 ± 0.70	$p \leq 0.05$
SOD	10	2.0 ± 0.67	NS

TABLE 3. *The Degree of Adhesions in Animals with Peritonitis, No Solid Feces, and a 2-cm Segment of Necrotic Ileum*

Treatment Group	N	Adhesions (mean ± SD)	Significance
Control	10	1.4 ± 0.7	—
Heparin	10	0.5 ± 0.53	$p < 0.01$
Ibuprofen	10	1.0 ± 0.47	NS
SOD	10	1.3 ± 0.48	NS

undergoing pelvic surgery. Despite these publications, resection of the peritoneum continued to be thought of as one of the most important factors in the production of adhesions. It was not until the publication of Ellis in 1962 that doubt was cast on this hypothesis.[10] He demonstrated that the most potent stimulus to the production of adhesions was tissue ischemia. Because tissue ischemia is often associated with peritoneal resection, it would not be surprising that some confusion might have existed as to the most important causative factor.

Although peritoneal healing has often been compared to cutaneous wound healing, recent studies have shown substantial differences. Ellis et al.[11] demonstrated that the area of peritoneal wound becomes covered by a fibrinous exudate. This event precedes an infiltration of monocytes, histiocytes, and polymorphonucleocytes. By the third day, many of these cells have disappeared and the surface becomes covered by a continuous layer of cells. At this point, fibroblasts invade the surface, and by the fifth day, the superficial layer is made up of flattened cells that closely resemble the adjacent peritoneum. By the second week, the area of injury is covered by a thin layer of fibrous tissue and a smooth mesothelium indistinguishable from the original surface. It is clear from the work of Ellis et al.[11] that the ingrowth of cells does not occur from the periphery of the wound but probably by seeding from the peritoneal cavity.

When the peritoneum has been injured by a bacterial agent or by mechanical methods, areas of ischemia are produced. Necrotic tissues excite an outflowing of fibrinogen from the peritoneal surface. Because the surface area of the peritoneum is roughly similar to the cutaneous surface, a large amount of fibrin can be deposited in a short period of time. The progression of the process is dependent upon the delicate balance between the outpouring of fibrinogen and the plasminogen-mediated resorption process. Many of the drugs that have been proposed to ameliorate the production of adhesions impact on this equation.

TABLE 4. *The Degree of Adhesions in Animals with Peritonitis, Solid Feces, and a 2-cm Segment of Necrotic Terminal Ileum*

Treatment Group	N	Adhesions (mean ± SD)	Significance
Control	10	1.9 ± 0.74	—
Heparin	10	1.4 ± 0.52	NS
Ibuprofen	10	1.6 ± 0.7	NS
SOD	10	1.9 ± 0.57	NS

Filmy adhesions are the early result of the fibrin deposition. Dense adhesions are the result of the ingrowth of mononuclear cells that deposit collagen within the fibrin matrix. The dense adhesions play a role in the revascularization of ischemic tissue. Anti-inflammatory agents such as adrenocorticotrophic stimulating hormones, corticosteroids, or cytotoxic agents have been administered in an attempt to reduce this phase of adhesion maturation. Although some authors have shown these to be effective,[12,13] they have substantial side effects.

Nonsteroidal anti-inflammatory agents have been evaluated and found to produce similar effects without the compromising host immunity. Of these agents, the most widely tested has been ibuprofen. Siegler et al.[14] demonstrated a significant reduction in adhesion formation in the rabbit uterine horn when treatment groups were compared to control. There was no significant difference between those animals treated with dexamethasone or with ibuprofen. In subsequent studies using a similar model, Bateman et al.[15,16] demonstrated that adhesions secondary to either trauma or ischemia could be significantly reduced by treatment with ibuprofen. Nishimura et al.[17] further delineated these observations by demonstrating that in a model utilizing standardized abrasion, ischemia, or crush injury to the rabbit uterine horn, ibuprofen in a dose of 70 mg/kg immediately and 6 hours postoperatively decreased the incidence of adhesion formation. In subsequent studies they showed that a relationship existed between the dose of ibuprofen and the degree of adhesion formation.[18,19] These studies also demonstrated that the timing of therapy was important. Animals that received a high dose of ibuprofen within 8 hours of the operation did better than those that received the same dose more than 12 hours after operation.

The mechanism of ibuprofen's action is unknown. There is evidence that the nonsteroidals block the prostacyclin cyclooxygenase system that converts arachidonic acid to the prostaglandin endoperoxides. Whether this has its effect by decreasing the leukotaxic effect of the stable thromboxanes or if it has its effect on the chemotaxic lipoxygenase has not been elucidated. Other hypotheses have been proposed, but confirmatory evidence as to the mechanism of action is still lacking.

Not all studies with nonsteroidal anti-inflammatories have documented a reduction in adhesion formation. O'Brien et al.[20] could not show an effect on adhesion formation, although a marked reduction in the histologic markers of post surgical peritoneal injury was demonstrated.

In this study, adhesions were not prevented by ibuprofen. In fact, adhesions were greater and survival less when viable intestine was left in association with fecal contamination. The lack of demonstration of a protective effect may be related to the size of the dose of ibuprofen administered. In previous studies by Nishimura, the smallest dose to be associated with suppression of adhesion production was 35 mg/kg/d. If the results are to be compared with human dosage, the amount of drug is massive. In this study, a different model was used, active infection was present, the entire peritoneum was evaluated, animals were male instead of female, and only 24 mg/kg/d of ibuprofen was administered. This dose is lower than that given by Nishimura, but more closely resembles a normal dose for humans. Any of these variables might have affected the outcome.

Because it has been shown that ischemia may be the single greatest cause of adhesion formation, this facet was explored in greater detail. Recent evidence suggests that oxygen-derived free radicals are abundantly produced in a ischemic tissue.[21] This production far exceeds the amount of free radicals produced during aerobic metabolism. In normal circumstances these radicals are neutralized by intracellular products known as scavengers.[22]

A free radical is a molecule containing an odd number of electrons rendering it extremely chemically reactive. If a radical interacts with a nonradical, yet another free radical is produced. This allows free radicals to participate in extensive chain reactions.[23]

When a tissue becomes ischemic, cellular metabolism switches from the aerobic to the anaerobic state. With reperfusion, there is a marked increase in the number of free radicals produced and a concomitant increase in tissue permeability. This increase in permeability may well be the cause of the outflowing of fibrinogen when the peritoneum is rendered anoxic.

The scavengers that normally occur in the body are in an intracellular position. Despite this, Granger et al.[24] demonstrated that in feline intestinal ischemia, the intravenous (I.V.) administration of superoxide dismutase can almost completely prevent the expected increase in capillary permeability.

In this study, 1800 IU of superoxide dismutase was administered 1 hour preoperatively and then once daily for 3 days. This regimen decreased the incidence of death in the treatment group but had little effect in the production of adhesions. From these observations, it can be deduced that either superoxide dismutase does not play a role in the production of adhesions, or that the timing of the administration of the agent may have been inappropriate. It is entirely possible that the agent may have been substantially cleared by the peritoneal cavity prior to the time of the insult. Because the next dose appears 24 hours later, the golden time for impact on adhesion production may have already passed. The fact that the death rate was significantly decreased suggests that superoxide dismutase does impact on the injury produced by peritoneal sepsis in the model tested.

Peritonitis was associated with an increase in the amount of peritoneal adhesions. In the control groups (no treatment), the addition of feces or necrotic tissue did not seem to increase the absolute number of adhesions when compared to peritonitis alone. It was interesting that the death rate was considerably higher in those animals with solid fecal contamination. The rate was unaffected by the presence or absence of a ligature on the pedicle of ileum. This may be related to the size of the bacterial inoculum, which in turn is related to time and rate of clearance of the bacteria.

It was surprising that the adhesions increased in number in the animals that had a viable segment of intestine. The effect of this on the death rate is unclear from the experiment. It was also interesting to note that heparin decreased the death rate in all groups except those animals with viable intestine and feces. This beneficial effect may have been related to an increased rate of clearance of fibrin and therefore an increased rate of clearance of bacteria. The only three deaths that occurred in the heparin-treated animals occurred in those with viable intestine and solid feces. The deaths occurred early and may have been related to factors other than sepsis.

Acknowledgment

We would like to acknowledge the contributions of Gregory B. Buckley, M.D. for his advice and the gift of the superoxide dismutase used in this study.

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DISCUSSION

DR. MARK A. MALANGONI (Louisville, Kentucky): I would first like to thank Dr. O'Leary for a very good presentation and also for providing me with a copy of his manuscript. I recommend his manuscript as an excellent review of the mechanisms that are involved in the pathogenesis of adhesions. In his manuscript, Dr. O'Leary emphasized that there are actually three components of the peritoneal adhesion response, and these relate either to inflammatory response to the bacteria themselves or to tissue ischemia.

His results show some points that I am going to ask some questions about, but first I would like to give some background on what he has discussed today.

First, when there is no treatment given, there is similar adhesion formation and adhesion response in all groups. When bacteria alone are provided—that is, when there are no feces in a nonnecrotic segment of ileum, regardless of treatment—there is also a similar response to adhesions. This would lead us to conclude that bacteria seem to be the principal effectors of the adhesion response, at least in this particular model.

When feces are added (and remember that feces tend to inhibit the clearance of bacteria), we see an increased mortality and no benefit from heparin on either survival or the adhesion response. When nonviable tissue as well as feces is present, nothing works very well, and in the absence of any type of antibiotic treatment or washing out of these bacteria, this is what we would expect.

I would like to ask some questions to help us determine the utility and applicability of this study to the clinical situation.

First, what kind of diet did these animals have? In general, rats are given a diet that is high in fiber, and this diet tends to give them a bacterial content in the large intestine and in the terminal ileum that is rather low in anaerobic bacteria. On the contrary, when a meat-fed diet is used, the anaerobic content is much higher, and this may, in fact, influence some of the results that Dr. O'Leary obtained.

Also, did you do any cultures to define the inoculum either by the species of bacteria involved or the numbers of organisms? This information would be useful to help us compare this model with other models of peritonitis, both monomicrobial and polymicrobial, and would help determine its utility.

Second, based on your results, do you believe there is any clinical role for heparin in patients, since in the presence of feces heparin alone did not decrease mortality?

And last, how do you propose that superoxide dismutase works in this model, particularly because this is not a model of ischemic with reperfusion, which has been the most common model investigated in the past for looking at the principal effects of superoxide dismutase.

DR. FRANCIS C. NANCE (Livingston, New Jersey): Dr. O'Leary was kind enough to share his manuscript with me, and I recommend it to you for reading because it is an elegantly designed study and a nice review of the various types of experimental models that have been used in trying to attack this problem of adhesions.

However, I come away from this paper with some frustration because after reading the paper or listening to the presentation, I don't feel myself any closer to having an answer to the adhesions problem.

Dr. O'Leary has used heparin, ibuprofen, and SOD for prevention of adhesions. I am not sure that, on the basis of the data, almost any other method is not better than his.

His results are somewhat confusing to me. Heparin increased adhesions in one of his groups, and decreased them markedly in the other. Heparin seems to be the most promising of the agents he studied, and I would like to ask him to try to elaborate on how heparin is working in this case, and whether he thinks that in this adhesion model, there is any future in heparin.

DR. J. P. O'LEARY (Closing discussion): Let me discuss Carter's criticism first. I have trouble and do not understand, Dr. Carter, exactly why the animals with heparin onboard and solid feces and nonviable bowel—which is the group that had increased adhesions—did less well. All the animals died and were autopsied either at the time of death or the time of being killed. I think what happened was that when some of the animals died, we had the chance to examine their peritoneal cavity early and therefore saw the early type of fibrinous adhesions that one will often see. That is probably why the adhesion score was higher.

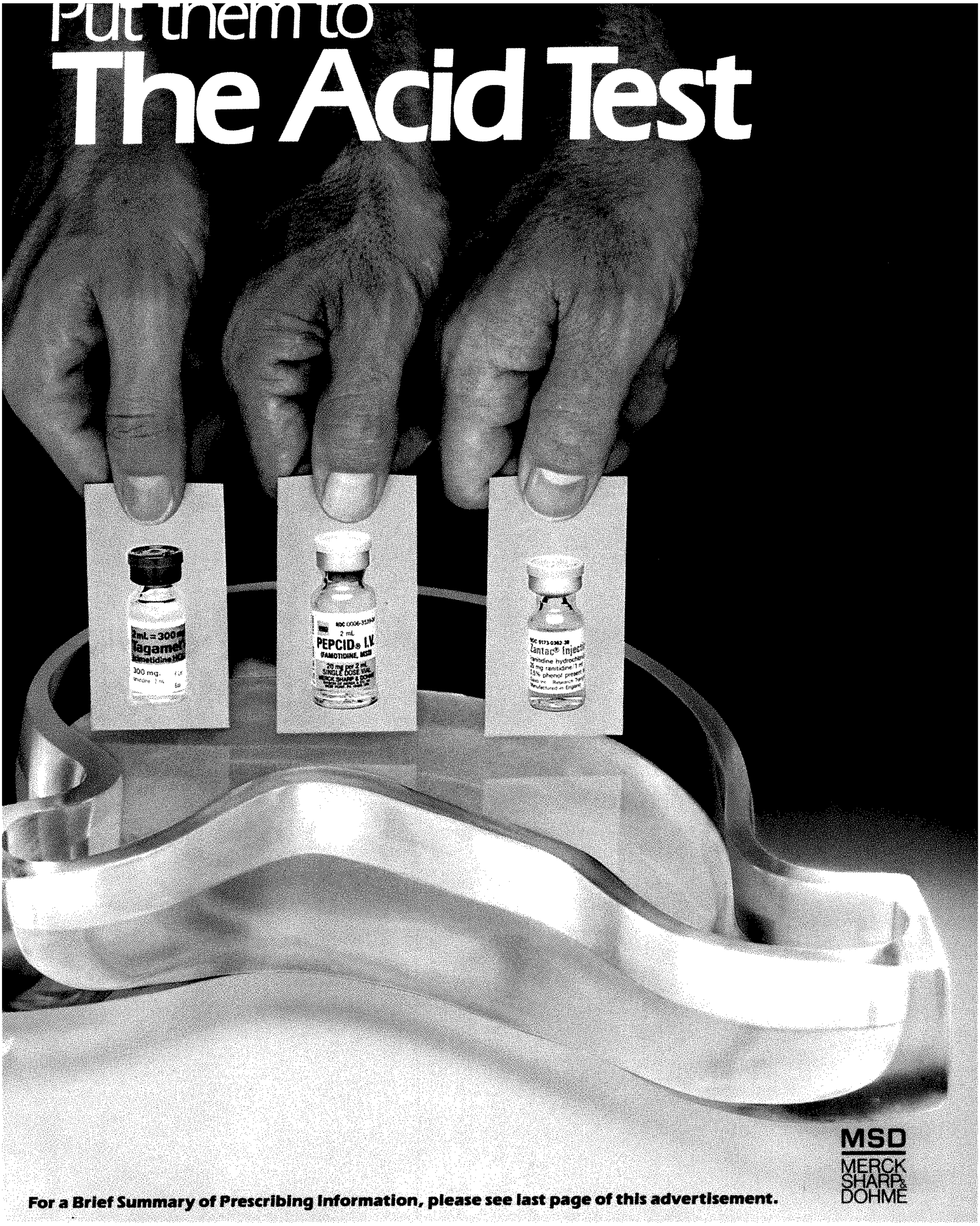
Now, why they died is still not clear to me. I would like to believe that maybe they were bleeding as a result of the amount of heparin that we used (although we used the same dose of heparin throughout), but I do not have an explanation for this.

The diet that the rats received, Dr. Malangoni, was a regular chow diet. We did do cultures. We did not include those cultures in the report because it was such a mixed bag of cultures.

You are correct in deducing that we discovered less aerobes than one might have anticipated, and I believe that this is because we were using the rat-chow diet.

Do I think there is a clinical role for heparin? I think it is too premature to say that; but then I look across our operating rooms and see vascular surgeons who mistreat the small intestine in the worse conceivable way while they perform aneurysectomies. Yet those patients don't seem to return with the incident of bowel obstruction that my simple colectomies or resection of small bowel seem to cause patients to return with. Therefore, there may be a clinical role for the use of heparin, but at this particular point, based on the data in the literature that I know of, I could not make that proposal.

With regard to SOD, superoxide dismutase: it is not clear to me how this scavenger works, since it would have to be intracellular to clear the radicals, and yet we are administering it extracellularly. Earlier data from members of our own organization have shown that this is, in fact, effective, and it is effective through intravenous administration. Yet I am not sure of its site of action.



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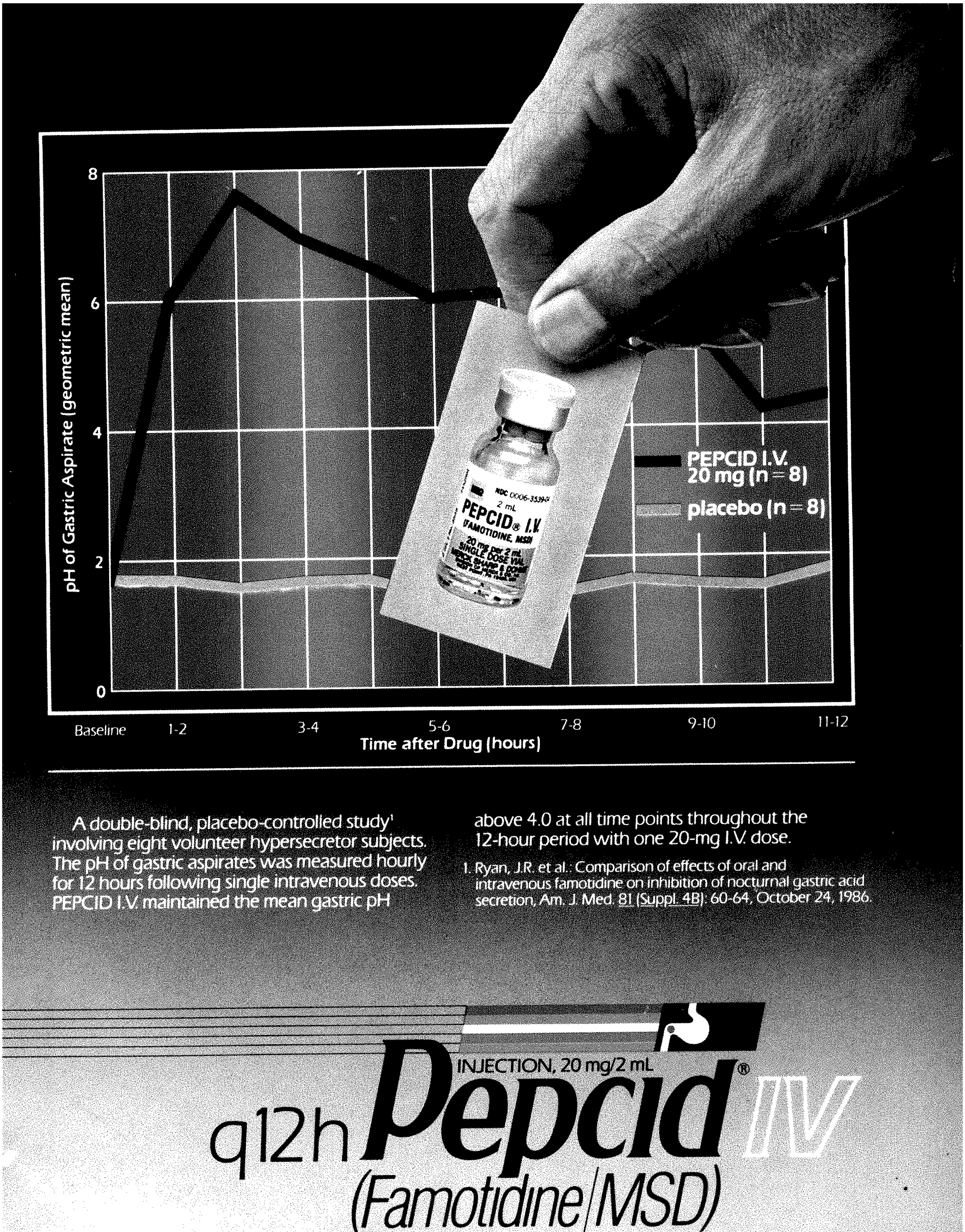

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[1] Ryan, J.R. et al.: Comparison of effects of oral and intravenous famotidine on inhibition of nocturnal gastric acid secretion, Am. J. Med. 81 (Suppl. 4B): 60-64, October 24, 1986.

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Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas): The dosage varies with the individual patient; the recommended adult oral starting dosage is 20 mg q6h, but some patients may require a higher starting dosage. Dosages should be adjusted to individual patient needs and continued as long as clinically indicated; up to 160 mg q6h have been administered to some patients with severe Zollinger-Ellison syndrome.

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Surgical Treatment of Acute Traumatic Tear of the Thoracic Aorta

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Acute traumatic tear of the thoracic aorta is a severe injury with a high mortality rate. This condition requires expeditious evaluation and prompt surgical intervention in order to improve patient survival. The experience at the authors' institution from 1971 to 1987 includes 41 patients who sustained acute traumatic tear of the thoracic aorta and reached the hospital alive. The purpose of the study was to evaluate the surgical management of this injury with regards to mortality rate and the incidence of spinal cord injury. Five patients died from exsanguination before definitive repair could be undertaken. Thirty-six patients had repair of traumatic aortic tear in the area of the isthmus. Nine patients were operated upon with the clamp and sew technique, 20 patients had a heparin-bonded shunt placed, and seven patients were treated by repair with cardiopulmonary bypass. There were five operative deaths that were not related to the technique employed. Two patients without preoperative evidence of spinal cord injury developed paraparesis. No patient had postoperative paraplegia. Despite rapid transport, expeditious evaluation, and emergency thoracotomy, some patients die from exsanguination prior to definitive repair. Even with the provision of distal aortic perfusion during clamping, the risk of spinal cord injury is not eliminated.

IN THE UNITED STATES there are approximately 100,000 deaths per year secondary to trauma; 25% of the deaths are the result of blunt injury to the chest. It is estimated that about one-third of the patients who suffer blunt chest trauma will have a traumatic tear of the thoracic aorta.[1] Greendyke[2] found that 16% of automobile accident fatalities were due to aortic rupture. Aortic injury is most frequently seen as a consequence of high speed deceleration, usually as a result of motor vehicle accidents. This injury has also been seen after falls from heights, airplane accidents, kicks by animals, and sudden burial by landslide.[3]

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It is well known that most patients who sustain an aortic tear die at the scene. However, in approximately 15–20% of patients free rupture and exsanguination are prevented by the aortic adventitia and surrounding mediastinal structures. These patients survive long enough to reach the hospital. Without definitive treatment most of those who reach the hospital alive die within one week.[4] Therefore, patients with acute aortic tear require rapid and thorough evaluation and expeditious treatment to maximize their chances for survival.

Since the initial success in repairing an acute tramatic aortic tear in 1959 by Karl P. Klassen,[5] there has been continued interest in the development of operative techniques to provide expedient repair while minimizing distal organ ischemia. Various methods have been used including no shunt (clamp and sew),[6-11] heparin-bonded shunts,[12-16] and various bypass techniques with systemic heparinization.[17-20] This report is limited to patients operated upon during the acute phase of their injury prior to healing of the aorta and development of a chronic aneurysm (<7 days). A retrospective analysis of this experience was undertaken to evaluate the type of injury incurred, the influence of time from injury to repair, and the incidence of spinal cord injury and mortality rate relative to the operative technique employed.

Materials and Methods

At the authors' institution between July 1971 and July 1987, 41 patients were seen after sustaining blunt chest injury and acute aortic tear in the area of the aortic isthmus. Thirty-three patients were male and eight were female. Age ranged from 10 to 79 years with a mean age of 33 ± 16.8 years. Of the 41 patients, 29 were less than

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TABLE 1. *Clinical Features*

Symptoms	
Chest pain	23 (55)
Shortness of breath	9 (21)
Interscapular pain	2 (4)
Hoarseness	1 (2.3)
Physical findings	
Hypotension	19 (45)
Pulse discrepancy	17 (40.5)
External chest trauma	16 (38)
Acute coarctation	3 (2)
Systolic murmur	2 (4)
Paraplegia	1 (2.3)

Values in parentheses are percentages.

TABLE 3. *Associated Injuries*

Orthopedic	
Femoral fracture	12
Hip fracture	8
Mandible fracture	6
Pelvic fracture	4
Neurologic	
Closed head injury	11
Skull fracture	5
Abdominal	
Ruptured spleen	6
Liver laceration	4
Other	2

40 years of age. Forty patients suffered deceleration injuries. Thirty-seven were involved in automobile accidents, two in motorcycle accidents, and one in a go-cart accident. One patient was a pedestrian who was struck by a car.

Thirty-one patients arrived by ambulance, and ten arrived by helicopter. Only 12 patients were seen from 1971 to 1979, while 29 were seen between 1979 and 1987.

The history and physical examination provided valuable information but were by no means diagnostic. The symptom most often elicited was retrosternal chest pain (23 of 41 patients). Nineteen patients were hypotensive, with a systolic pressure less than 100 mmHg, on presentation in the emergency room. Pulse discrepancy and evidence of external chest trauma were frequently encountered physical findings, occurring in 17 and 16 patients, respectively (Table 1). Three patients had no femoral or leg pulses associated with arm hypertension. One patient had paraplegia on admission.

Thirty-five patients had roentgenographic findings suggestive of aortic injury, but six patients had a chest roentgenogram that was interpreted as normal. A widened mediastinum was seen in 35 patients. Fourteen patients had multiple rib fractures, and obscuration of the aortic knob was seen in ten patients. The most frequent radiographic findings are listed in Table 2.

The severe force that resulted in aortic tear caused significant associated injuries in all but two patients. Twenty-eight patients had major fractures, with femoral fractures being the most common. Sixteen patients experienced significant head trauma. Twelve patients required exploratory laparotomy; 10 of these were performed prior to thoracotomy in unstable patients with exsanguinating intraabdominal hemorrhage. Splenectomy was the procedure most often performed (Table 3).

TABLE 2. *Most Frequent Chest Roentgenogram Findings*

Wide mediastinum	35
Multiple rib fractures	14
Left pleural effusion	14
Blunt aortic knob	10
Normal chest roentgenogram	6

All patients were treated by emergency aortography, which was diagnostic in all instances except one. This patient's initial aortogram was thought to be within normal limits. Serial chest radiographs documented a widening mediastinum, prompting a second aortogram, which documented an aortic isthmus tear.

It has been the authors' policy to proceed with emergency thoracotomy and repair of the aortic tear once the diagnosis has been established. Thoracotomy is delayed only in patients with life-threatening intracranial injury or exsanguinating intra-abdominal hemorrhage. All patients except four were operated upon within 24 hours of injury. These patients were transferred from outside institutions at 2, 3, 4, and 7 days after their injury. Twenty-five patients were operated upon within 8 hours of their injury.

All patients had general anesthesia with a double-lumen endotracheal tube. Patients were monitored with a central venous pressure line, right radial arterial line, electrocardiogram, and Foley catheter. A standard posterolateral thoracotomy through the fourth or fifth intercostal space was performed with resection of a rib when necessary. Great care was taken to gain proximal and distal control prior to entering the mediastinal hematoma. Depending on the surgeon's preference and the patient's condition, a technique of no shunt, heparin-bonded shunt, or partial bypass was employed. A low porosity Dacron interposition graft was usually inserted. Two patients with limited noncircumferential tears were repaired primarily.

Results

Despite rapid transport and expeditious evaluation five patients did not survive to have their injury repaired. One patient with an aortic tear documented by arteriography in another hospital was transferred for definitive repair but died of exsanguinating hemorrhage immediately upon arrival in the emergency room. Two additional patients died in the arteriography suite from free rupture. Two patients had angiography but ruptured en route to the operating room. Emergency thoracotomy and control of bleeding was accomplished, but resuscitation was unsuccessful in both.

Thirty-six patients were treated by repair of traumatic tear of the thoracic aorta in the area of the isthmus (Table 4). The nine patients in the clamp and sew group had a mean cross-clamp time of 35.7 minutes. There was one death for a mortality rate of 11.1%. The mean cross-clamp time for the 20 patients in the shunt group was 44.3 minutes. Two patients died (mortality rate: 10%). The shunt was placed from the aortic arch to the descending thoracic aorta in 18 patients, and it was placed from the left ventricular apex to the aorta in two patients. The seven patients in the partial bypass group had a mean cross-clamp time of 39.4 minutes. There were two deaths in this group for a mortality rate of 28.6%.

Of the 36 patients treated by repair five died, resulting in an overall mortality rate of 13.9%. The one death in the clamp and sew group occurred in a patient who initially required urgent laparotomy for exsanguinating intra-abdominal hemorrhage. Following laparotomy an aortogram documented a tear in the aortic isthmus. The patient was returned to the operating room hypothermic, acidotic, and hypotensive. Ventricular fibrillation occurred when the aorta was cross-clamped. Repair and resuscitation were unsuccessful.

Both deaths in the shunt group occurred under similar circumstances. Each patient had extensive dissection of the aorta both proximally and distally making repair difficult and resulting in exsanguination in each case.

There were two deaths in the partial bypass group. Both patients exhibited loss of distal pulses, metabolic acidosis, and hypotension after operation. One patient with an associated myocardial contusion died of right ventricular rupture and exsanguination after cross-clamping the aorta. The other patient had preoperative pulmonary edema, left ventricular failure, hypotension, and acidosis. When the aortic cross-clamp was applied ventricular fibrillation occurred. Repair and resuscitation were unsuccessful.

One patient presenting with paraplegia died intraoperatively. There were no instances of postoperative paraplegia. Two patients with normal motor function of the lower extremities prior to operation had paraparesis after operation. Both patients were in the shunt group. One patient had a shunt from the left ventricle to the descending aorta. Cross-clamp time was 50 and 75 minutes, respectively, for these two patients. Each was ambulatory with assistance at discharge and doing well 1 year after repair.

TABLE 4. *Technique of Repair and Results*

Technique	Clamp Time (min) (mean)	N	Mortality Rate	Spinal Cord Injury
Clamp and sew	35.7	9	1 (11.1)	0
Shunt	44.3	20	2 (10.0)	2
Partial bypass	39.4	7	2 (28.6)	0

Values in parentheses are percentages.

There were no postoperative deaths in those patients who survived operation. Morbidity rate was related to concomitant injuries rather than to the aortic repair. There was no statistically significant difference in survival of those patients operated upon less than or greater than 8 hours from the time of injury.

Discussion

The clinical presentation is quite variable in patients with traumatic tear of the thoracic aorta. More than 90% of the patients are involved in automobile accidents.[9,10,20-22] Physical examination may be helpful, but it may be misleading. Some patients have no evidence of thoracic trauma, while others have multiple rib fractures, hemothoraces, or flail chest. The triad of findings mentioned by Symbas et al.[19] are: (1) difference in pulse amplitude between upper and lower extremities; (2) hypertension in the upper extremities; and (3) widening of the mediastinum on the chest roentgenogram. These are helpful in making the diagnosis, but these findings are not present uniformly.

The initial chest roentgenogram may be the only indication of aortic injury. As documented by virtually all series[9-11,20-23] as well as this series, widened mediastinum is the most common finding in patients with traumatic tear of the aorta. An abnormal contour of the aortic knob is also seen frequently. Although multiple rib fractures are frequently associated with aortic tear, it has been shown that acute traumatic tear of the thoracic aorta may occur in the absence of rib fractures.[24] It has also been shown that upper rib fractures alone are not associated with a high incidence of aortic rupture.[25]

There are many roentgenographic signs that various authors have suggested as possible clues to the presence of acute traumatic tear of the aorta.[26] However, it must be kept in mind that some patients with an aortic tear have a virtually normal chest roentgenogram.[21,27] In the present series six patients with a documented aortic tear had a chest roentgenogram that was initially interpreted as normal. It seems reasonable that even in the absence of roentgenographic signs suggesting an aortic tear, any patient with a history of a high speed deceleration accident should be strongly considered as a potential candidate for aortography.

Aortography remains the generally accepted standard test for the diagnosis of this injury. In this hospital of every 100 aortograms performed approximately 10–12% are positive. It has been suggested that of all patients who undergo aortography in an attempt to document the presence or absence of an acute traumatic tear of the thoracic aorta, approximately 10–20% of the patients will have a positive study.[28]

Recently there has been increased interest in computed tomography (CT) as a method for diagnosing acute tear of the thoracic aorta. CT signs of acute tear include increasing caliber of the aorta, internal displacement of intimal calcification, visualization of an intimal flap, or visualization of the false channel.[28] To date no prospective randomized trial has been published comparing CT to arteriography in regards to sensitivity and specificity of diagnosis of acute aortic tear.

It has been the authors' practice to undertake prompt evaluation and management of multisystem injuries in these patient who are often in critical condition. The majority of these patients were operated upon within 8 hours of their injury. Thoracotomy and repair of aortic tear is delayed only in those patients with life-threatening intracranial injury or exsanguinating intra-abdominal hemorrhage. The necessity of prompt intervention is clearly evident by the fact that five patients exsanguinated in the hospital before definitive repair could be undertaken.

There is a divergence of opinion as to the best operative technique for avoiding distal organ ischemia while minimizing mortality rate. Presently, there are three accepted techniques for managing traumatic tear of the thoracic aorta: clamp and repair, external heparin-bonded shunt, and partial or complete bypass. Many authors have stated that the simple clamp and sew technique is safe and does not result in an increased incidence of paraplegia when compared to other methods.[9–11,29,30] This technique may be considered when the aortic injury seems limited and the surgeon is reasonably certain that repair can be accomplished quickly, with a cross-clamp time less than 30 minutes. Katz et al.[31] documented that there is an incrementally increased risk of spinal cord injury when the cross-clamp time exceeds 30 minutes.

In recent years the use of an external heparin-bonded shunt has been preferred by the authors. It usually provides adequate decompression of the proximal aorta and adequate flow in the descending aorta without the necessity of systemic heparinization, which may be dangerous in certain patients with multisystem injuries. Two of these patients who were repaired with this method developed paraparesis. In both patients there were technical difficulties with the repair due to extensive dissection and aortic injury, and the clamp times were prolonged. This prolonged clamp time is the probable explanation of the development of the spinal cord injury. On the other hand, there could have been inadequate flow through the shunt. One of the patients was repaired with a left ventricular apex to aorta shunt. Marvasti et al.[14] found a higher incidence of spinal cord injury when the proximal cannulation site was the left ventricle. They attributed this to lower mean pressure in the left ventricle and possible occlusion of the shunt tip during systole. They also noted that the shunt could be malpositioned when placed in the left ventricle, thus decreasing flow through the shunt.

Bypass techniques were used more commonly in the authors' earlier experience. Most authors have now abandoned bypass techniques because of concerns regarding total body heparinization of multiple injury patients. One recent large series supports the use of extracorporeal circulation. Pate[20] reported 59 patients with acute aortic tear at the isthmus. Forty-seven of these patients had repair using a pump oxygenator. There were two deaths and one case of paraplegia. Neither of the deaths was due to exsanguination. However, one death was attributed to a head injury in a patient who had received heparin during bypass. In this excellent series there was a mortality rate of approximately 5%. Other series have reported a mortality rate of approximately 15–30% for patients undergoing repair of aortic tear on cardiopulmonary bypass.[11,22]

In the authors' experience, the mortality rate is not influenced by the technique of repair. Rather, mortality rate is related to the presence or absence of extensive dissection, which makes repair and hemostasis difficult, and to the preoperative condition of the patient. Those patients who reached the operating room in stable condition and who did not have extensive dissection all survived.

It has been suggested that several adjuncts might possibly improve spinal cord protection during clamping of the aorta. In the experimental laboratory systematic evaluation of the use of corticosteroids, mannitol, free radical scavengers, and thiopental was performed.[32,33] Only thiopental has been shown to provide a statistically significant reduction in the frequency of paraplegia. In recent years it has been the authors' practice to administer 20 mg/kg thiopental intravenously to patients with traumatic tear of the aorta prior to application of the aortic clamps.

Recently, a new technique for monitoring somatosensory cortical evoked potentials has been developed in the experimental laboratory and applied clinically. Lashinger et al.,[34] Coles et al.,[35] and Oka and Miyamato[36] have reported their experience with this technique. Their results seem promising, but because of the technical sophistication of the method, it has been difficult to duplicate results, and the method has not gained wide acceptance. The authors' efforts have concentrated on accurate, expeditious repair of the torn aorta in the expectation of minimizing cross-clamp time and blood loss. The repair is performed with meticulous attention to detail in order to achieve good hemostasis and avoid reclamping the aorta.

Acute traumatic tear of the thoracic aorta is a surgical emergency that requires a high index of suspicion, prompt diagnosis, and urgent operative intervention. Repair should be performed in an accurate, expeditious manner. Despite the use of techniques to limit distal organ ischemia, the risk of paraplegia is not eliminated.

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DISCUSSION

DR. KENNETH MATTOX (Houston, Texas): I want to congratulate Dr. Bender and his coauthors for a well prepared and beautifully presented paper. Some of my comments relate to the manuscript, which was provided to me well in advance.

This is a retrospective review of three techniques, historically randomized by national evolutions in practice trends and by physician preference. Because of numerous changes in perioperative management, injuries repaired on cardiopulmonary bypass early in this series cannot really be compared with those repaired during this decade, and this is true of all series in the literature.

This paper supports the composite literature review demonstrating that none of the current acceptable techniques of protection should be either championed or condemned. Patients, families, and plaintiff lawyers should understand that no technique eliminates postrepair paralysis. Recent series, however, have demonstrated that the lowest mortality and paraplegia are actually in the clamp/repair group. Neither the Gott shunt nor the pump protects the patient from death or paralysis, and both actually make this complex operation much more difficult.

This manuscript, like many others, focuses on a frequently quoted 30-minute "optimal" clamp time. These statements may not only be fallacious, but also point to something unobtainable, forcing a hurried operation and inviting imprecision and litigation. The length of the cross clamp time is, in truth, a function of the extent and complexity of the injury, and not necessarily a reflection of the surgeon's technical prowess and dexterity. Virtually all series, including the one reported here, cite mean clamp times greater than 35 minutes, with a very wide standard deviation. Our own clamp times average 38 minutes. There are reported clamp times as long as 110 minutes, with documented distal aortic perfusion pressure at 20 mm of mercury without the appearance of paraplegia. Also, clamp times of less than 15 minutes may be associated with paraplegia.

Because of a false sense of security, when a shunt is used, clamp times tend to be longer than with clamp repair technique. This paper, like many others, states that if a surgeon anticipates a clamp time longer than 30-minutes a shunt should be considered in order to (1) protect the patient from paralysis, and (2) protect the surgeon from lawsuit. Unfortunately, both statements are not true.

Except in sophisticated research centers, in the case of acute traumatic aortic transsections, which is usually a nocturnal event, somatosensory-evoked potential measurement is difficult, cumbersome, misleading, and inconsistent. Until solid, new, conclusive data is presented, our publications should cease to cite its use, or else we all will be legally required to purchase and utilize this unproven and confusing monitoring technique.

This lesion is one of the most litigious in vascular surgery. Twenty-five per cent of patients with this injury and paraplegia are now filing lawsuits. These suits are frequently supported by sanctimoniously rigid statements—some made even by members of this Association. Numerous unfounded, emotionally polarized but published statements concerning protection, clamp times, and monitoring are loudly quoted in court, with millions of dollars in settlements and judgments.

Carefully hidden in the many papers on this injury are notations on complications from the shunt itself: displacement, inadequate flow, postoperative bleeding, aneurysms, and many others. One question: Did you have any shunt-related problems that were found in your shunt patients?

I congratulate Dr. Bender and his coauthors for reaffirming the lethality and complexity of this injury, and for documenting the safety and utility of all acceptable current techniques.

DR. JAMES D. HARDY (Jackson, Mississippi): I congratulate Dr. Bender on his excellent presentation of his impressive results. Our experience at the Hospital of the University of Mississippi has been very similar to his.

When I received the program, I called Vanderbilt to ask whether or not their group planned to show a movie. They did not.

May I have the movie, please. (A movie was shown).

This young man had been in an automobile accident and sustained a fracture of the femur and a head injury. The widened mediastinum exhibited on chest x-ray prompted an aortogram, and as you can see, there were two tears in the aorta: one at the most common site, just distal to the left subclavian artery, and another about 10 cm above the diaphragm. Over the years, we have seen traumatic aneurysms at various sites, extending from the aortic valve to the diaphragm.

Here the movie shows the subpleural hematoma in the mediastinum and, after incising the parietal pleura, an aortic clamp's being applied just adjacent to the left subclavian artery and a second clamp below the apparent level of the aortic injury. Note the preservation of the vagus, recurrent, and phrenic nerves. Now the hematoma has been evacuated and some blood is leaking through the aortic adventitia, the only layer of the aortic wall still intact. The intima and the media, still one unit, were divided completely by the deceleration accident, and the ends of the aorta (except for the adventitia), have retracted from each other about 5 cm. With a complete tear such as this, we do not attempt a primary repair; we insert a fabric graft, here Dacron™, to restore aortic continuity. Incidentally, if needed, Teflon felt backing can be very effective in achieving secure hemostasis at each end of the fabric graft.

Now we have removed the aortic clamps, and you can see that the suture line hemostasis is satisfactory.

(Please stop the film.)

The lateral tear just above the diaphragm was then readily closed, using Teflon felt backing of the sutures.

Again, our data for the management of traumatic aortic aneurysms at the level of the isthmus are very similar to those presented by Dr. Bender and his colleagues. I was gratified to find that, although six different staff surgeons performed or supervised the operations, since 1970, our results have been almost uniformly satisfactory when the lesion was at the level of the isthmus, when the patient was in stable condition at the time of thoracotomy and when the patient had no other major injury, such as head or liver trauma.

Lastly, I personally heparinize the patient while the clamps are on the aorta. I have used aortic bypass less and less in recent years.

I have enjoyed this paper very much.

DR. FREDERICK GROVER (San Antonio, Texas): I would like to compliment Dr. Bender and his co-authors on a fine study of a difficult problem.

During our 15 years together in San Antonio, Kent Trinkle and I have had a similar number of patients with this injury.

We would agree that a high index of suspicion and a prompt diagnosis are imperative, and angiography should be performed very early in patients suspected of this injury. This has been helpful in our experience, both for diagnosing the lesion and for exclusion of patients with a wide mediastinum who, indeed, do not have the injury. In addition, it identifies the location of the injury. We have also seen avulsion of the innominate artery from the ascending aorta, which, of course, requires a completely different incision.

Some people are now advocating the use of CT scanning, and I wonder how the Nashville group feels about this.

Our current policy in regard to operative technique is to place a tubular graft in all patients with complete transection of the aorta, but sometimes to perform a primary repair in those patients with a partial transection. We went through a phase when we were trying to do primary repairs in all patients and had some technical problems with tearing and bleeding when trying to pull the ends of a completely transected aorta together without a graft. In the past, we have also attempted to use intraluminal prostheses in these patients, thinking that it might shorten our cross-clamp time, but have been disappointed because most of them have had too small an aorta to use these grafts, and too short of a proximal portion of the aorta distal to the subclavian before the location of the transection. I would be interested if you have used any of these intraluminal grafts, and would like to learn about your technique regarding insertion of the graft.

The incidence of paraplegia is of concern to all of us. We have had patients with paraplegia in spite of having been on partial bypass and having had an expeditious operation. Therefore, we began using the "clamp and sew technique," as popularized by the Baylor group; yet in the past year, we have had two patients with a paraparesis in whom we used this technique, despite there being only 30 minutes of cross-clamp time.

There is one question I would like to ask in regard to this. In an attempt to control proximal hypertension we give intravenous nitroprusside when we use the "clamp and sew" method, but when we monitor the dorsalis pedis pressure distally, we sometimes find that the distal pressure is alarmingly low. Do you monitor the distal pressure, and do you use nitroprusside? How do you counteract the presumed decrease in collateral flow when treating these patients with intravenous nitroprusside?

Because of these recent incidences of paraparesis, we are currently considering using the Biomedicus pump with left atrial to femoral artery bypass. Have you had any experience with this?

My final question concerns the prioritizing of injuries. You alluded to the fact that in somebody who was bleeding heavily from the abdomen, you would explore the abdomen first. How do you prioritize these injuries? What about the patient who has a dilated pupil and a neurologic injury?

Again, I enjoyed your paper very much on this difficult management problem.

DR. GEORGE C. KAISER (St. Louis, Missouri): Stimulated by the abstract of Dr. Bender and his associates, at St. Louis University we reviewed our experience with traumatic transection of the aorta.

From 1979 to the present, we have operated on twenty-six patients, with an operative mortality of 15%. A shunt was used in 54%; the clamp and saw technique was used in the remainder. We have not used a bypass in any of these patients.

One of 12 (8%) of those treated without a shunt died, whereas three of 14 (21%) died in whom a shunt was used. Paraplegia occurred in one patient in the group treated without shunts, and likewise in two in whom the shunt was used.

Of the two patients with paraplegia in the shunted group, one had extensive cerebral injury requiring multiple craniotomies; the other, with a cross clamp time of 37 minutes, had associated subluxation of L-2 and 3. In the single patient of the nonshunted group who had paraplegia, the cross clamp time was 35 minutes. As others have already alluded to today, the use of a shunt was believed, in some instances, to have contributed significantly to the morbidity and mortality of the procedure. The cross clamp time was greater in the shunted group, whether a graft was used or not.

Primary repair was used in 73% of the patients. The cross clamp time with primary repair averaged 34 minutes; it was 57 minutes with graft interposition. We prefer primary repair. It has been used without difficulty in the last 14 consecutive patients.

Our experience supports that which has been presented today. Clamping and sewing is an acceptable technique for managing these patients. It has a lower operative mortality and does not increase the incidence of paraplegia. We would further emphasize the importance and ease of primary repair.

I would like to ask a few questions about the use of the bypass technique. What are the usual cannulation sites? Is an oxygenator used? Is the patient heparinized? What do the authors feel is the indication for this technique?

I commend the authors for an excellent presentation of a fine clinical series.

DR. FRANK C. SPENCER (New York, New York): I will be brief, as there have already been several discussants. The large number of discussants well indicates the importance of this paper.

I certainly agree with Dr. Mattox that dogmatic statements about what is correct and what is incorrect must be avoided in this litigious society. A dogmatic statement, even though it represents an opinion held by less than 5% of practicing surgeons, can esaily be misquoted in a medicolegal trial and have a harmful influence on a lay jury. I am particularly aware of this fact, as I missed opening ceremonies yesterday because I was in court successfully defending myself in a case concerning a patient on whom I operated in 1975, 12 years ago, who subsequently developed a wound infection!

My first question concerns the fact that five of the nine deaths reported, nearly one half of the group, occurred before operation. This fact suggests a delay in surgical treatment that should be correctable. I imagine this delay resulted from not recognizing the diagnosis, or not realizing the necessity of immediate operation. With this type of injury, the constant risk of exsanguination is well recognized; so thoracotomy should be performed as quickly as possible.

Separately, I suppose that proximal control of the aorta was obtained as soon as the thorax was opened. This is best done by opening the pericardium and encircling the aorta before the hematoma surrounding the aortic laceration is touched.

My third comment concerns somatosensory monitoring. For over five years, this has been studied in detail at New York University and reported in several publications by Drs. Cunningham, Laschinger, and others. We consider somatosensory monitoring one of the most important developments in surgery of the thoracic aorta in recent years, although it seems too complicated for routine use with emergency problems, and although several basic questions remain unanswered. The available data, however, are very clear. If the proximal thoracic aorta is occluded and distal aortic pressure remains above 60 mmHg with intact sensory potentials, there seems to be very little risk of paraplegia. However, when sensory potentials disappeared for longer than 30 minutes, in over 50% of the patients in our series, paraplegia developed. Unfortunately, the method is so sensitive that technical mishaps may cause a loss of sensory potentials that are not due to ischemia. The main value of the technique, to date, is during elective surgery in controlled circumstances.

When the aorta is occluded, blood flow to the spinal cord through collateral channels requires a higher perfusion pressure because of the increased vascular resistance. Hence a perfusion pressure higher than 60 mm may be needed in some patients.

Over the past 20 years, the value of different types of aortic shunts has never been consistently proved because the data are inconclusive. These inconsistent results may have resulted from the fact that neither the flow rate through the shunt, nor the distal aortic pressure have usually been measured. A shunt, *per se*, gives no guarantee that an adequate volume of blood is being perfused into the distal aorta. This is the main defect with the ingenious Gott shunt, a significant technical advance in its time but, with the techniques now available, one that should be abandoned. Our data indicate that to maintain sensory potentials, flow through a shunt must be great enough to produce a distal aortic pressure near 60 mm or higher. For this reason, Nipride™ and other vasodilators are potentially dangerous unless very carefully used, because pressure in the distal aorta may be decreased below 60 mm.

In a recent publication, Dr. James Pate of Memphis well summarized previous reports concerning traumatic aortic injuries and paraplegia, and concluded that a shunt provides the greatest safety for the typical patient.

The vast majority of neurologic injuries that occur with traumatic rupture of the aorta are almost certainly due simply to infarction of the spinal cord from ischemia. The principal blood supply to the spinal cord arises between the tenth thoracic and second lumbar vertebra; thus, injuries of the proximal thoracic aorta are far away from the arteries critical to the spinal cord. With severe ischemia, infarction can probably occur in some patients within 20–30 minutes, depending upon the systemic blood pressure and the collateral circulation. Hence, the goal in future studies is either to develop a method of reconstruction of the injured aorta that requires less than 20 minutes of occlusion, or use a shunt that provides a large enough flow of blood to keep distal aortic pressure above 60 mm.

DR. ROBERT B. LEE (Closing discussion): Dr. Mattox, we would agree with virtually all of your statements. The medicolegal consequences of paraplegia are increasingly important. In the literature on this subject, many authors make dogmatic statements regarding spinal cord protection. Unfortunately, a definitive technique for providing fail-safe distal perfusion of the spinal cord has yet to be developed. It must be stated and restated that all methods, whether shunt, bypass, or clamp and sew, have been associated with cases of paraplegia. No method is foolproof.

We have had at least one shunt-related problem. One of our patients with paraparesis had a shunt placed from the left ventricle to the distal aorta. In our opinion, placement of the proximal cannula of the shunt in the left ventricle may result in insufficient distal aortic perfusion. This opinion is supported by the recently published experience of Dr. Marvasti. He states that the difference in the mean pressure in the left ventricle and the aorta may result in insufficient spinal cord perfusion. Also, it can be difficult to place a shunt accurately in the left ventricular apex so that it will function optimally.

We would like to thank Dr. Hardy for another in his series of surgical films. His work in surgical cinematography is always an excellent teaching device. We prefer to sew to the uninjured aorta after resection of the injured portion. Generally, we will resect to normal aorta and place an interposition graft. Virtually all of our patients had interposition grafts. Recently we have repaired two noncircumferential tears of the aorta by primary technique. We think that the decision of whether or not to use primary repair can be made only after the surgeon opens the aorta.

Dr. Grover's first question concerned the use of computed tomography in diagnosis of acute aortic disruption. No large series has been published documenting the treatment of this injury based on CT findings alone. However, CT does have a potential role in evaluation of this injury. Six of our patients had a chest x-ray that was initially interpreted as normal. If one's index of suspicion is high for such patients, then the CT does allow one to see if there is evidence of a mediastinal hematoma. This appears to be the CT scan's major indication at present.

As stated earlier, two of our patients had primary repair without an interposition graft. We would recommend primary repair only for patients with small, noncircumferential tears; we do not recommend it for extensive tears with distraction of the ends of the aorta.

Although nitroprusside will decrease proximal hypertension after aortic clamping, it will also lower vascular resistance and pressure in the remainder of the systemic bed. One must be judicious in using it, so as not to decrease distal perfusion to the spinal cord and kidneys. This decision is best made at the operating table, based on the amount of distention of the left ventricle, as well as pressure in the ascending aorta.

In regards to the BioMedicus™ centrifugal pump: this issue is addressed in a recent article by Dr. Oliver. He documented good results in nine patients in whom he used a heparinless Biomedicus pump. We have not used this modality.

Prioritizing injuries in a Level I trauma center is sometimes difficult. We have to remember that the most crucial injury is usually the thoracic aortic injury. Our data support this concept: despite a high index of suspicion and rapid transport to the arteriography suite, two patients experienced free rupture and exsanguination during arteriography. This fact re-emphasizes the unpredictable and sometimes fatal nature of this injury.

Dr. Kaiser, when we utilize partial bypass, we use the femoral vein to femoral artery technique. We usually reserve this option for patients who have significant metabolic acidosis and no contraindications to heparinization.

Dr. Spencer, we always use a retrograde femoral artery approach for the arteriogram catheter. The literature supports the safety of this technique. We agree that recognition and diagnosis are of the utmost importance.

The use of somatosensory evoked potentials for monitoring spinal cord function is frequently mentioned in the literature and has been mentioned by more than one discussant of this paper. We would agree with Dr. Mattox that this modality is not as useful in the acute setting as it may be in the nonemergency setting. It may have a role in the treatment of patients with an atherosclerotic thoracic aneurysm or coarctation. However, considerable expertise and judgment are required for analyzing the evoked potential data and altering the operative procedure on the basis of that data.

Although we use a shunt to provide distal perfusion for the majority of our patients, at present *no* technique provides the surgeon with certainty that distal organ ischemia and spinal cord injury will be prevented.

The authors would like to thank the Southern Surgical Association for the opportunity to present our data.

Reconstruction of Full Thickness Chest Wall Defects

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WILLIAM D. SPOTNITZ, M.D.,* and IRVING L. KRON, M.D.*

Over the last 5 years, 14 patients were treated by wide *en bloc* resection of chest wall tumors with primary reconstruction. There were nine females and five male patients with an age range of 31–77 years. All patients had a skeletal resection of the chest wall. An average of 3.9 ribs were resected in the patients treated. In three patients a partial sternectomy was carried out in conjunction with the rib resections. Chest wall skeletal defects were reconstructed with Prolene mesh, which was placed under tension. Soft tissue reconstruction utilized selected portions of the latissimus dorsi musculocutaneous territory with fasciocutaneous extensions beyond the muscle itself. Primary healing was obtained in all patients and secondary procedures were not required. The average hospitalization was 23 days. All patients survived the resection and reconstruction and were alive 30 days after operation. In selected patients the preservation of a portion of the innervated muscle *in situ* or the transfer of the muscle with the preservation of its resting length has maintained the majority of the muscle function.

SUCCESSFUL RECONSTRUCTION of thoracic wall defects should be provided ideally as an immediate one-stage procedure that provides structural stability and secure closure of the integument. Parham described his experience with thoracic resections for tumors of the bony chest wall in 1898.[1] In this monumental review he outlined all of the "cases of resection for malignant tumor of the thoracic skeleton" that he was able to find in the medical literature. The series began in 1778 and carried an overall 29.5% perioperative mortality rate. In his report, he expressed deep gratitude to both Fell[2] and O'Dwyer[3] for their contributions in the field of "intubation and forced respiration."

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Classification of tumors of the thoracic wall occurred during the early 1900s. Tumors of the chest wall such as sarcomas as well as intrathoracic tumors were defined by Lund,[4] Hedblom,[5] and Harrington.[6] By 1933, reviews by authors[4,5,7,8] indicated that more than 300 cases of chest wall resections for metastases as well as primary lung, breast, and rib tumors had been performed.

Chest wall structural stability has been obtained using fascia lata grafts as described by Watson and James.[9] Autogenous rib grafts were later used by Bisgard and Swenson.[10] These were used to reconstruct a resected sternum. They made a very important technical observation about the rib reconstruction in regard to structural stability. They distracted the ribs and placed the grafts under tension to provide firm anchorage for the grafts. Maier[11] advocated large cutaneous flaps from the medial portion of the opposite breast for central defects, and laterally based abdominal wall flaps for defects of the lower thoracic region. However, it is Campbell[12] who deserves a great deal of credit for clearly defining the use of the latissimus dorsi muscle flap for reconstruction of full thickness chest wall defects. He outlined both the nerve and the blood vessel supply through the thoracodorsal system (Fig. 1). He used the muscle to reconstruct an anterior chest wall defect and resurfaced it with a skin graft.

During the 1950s refinements were made in reconstructive techniques. Blades and Paul[13] stated that "large chest wall defects . . . can be treated satisfactorily, regardless of its size." Converse et al.[14] reconstructed a radiation ulcer over the heart with an abdominal flap carried on the forearm. Myre and Kirlin[15] focused their

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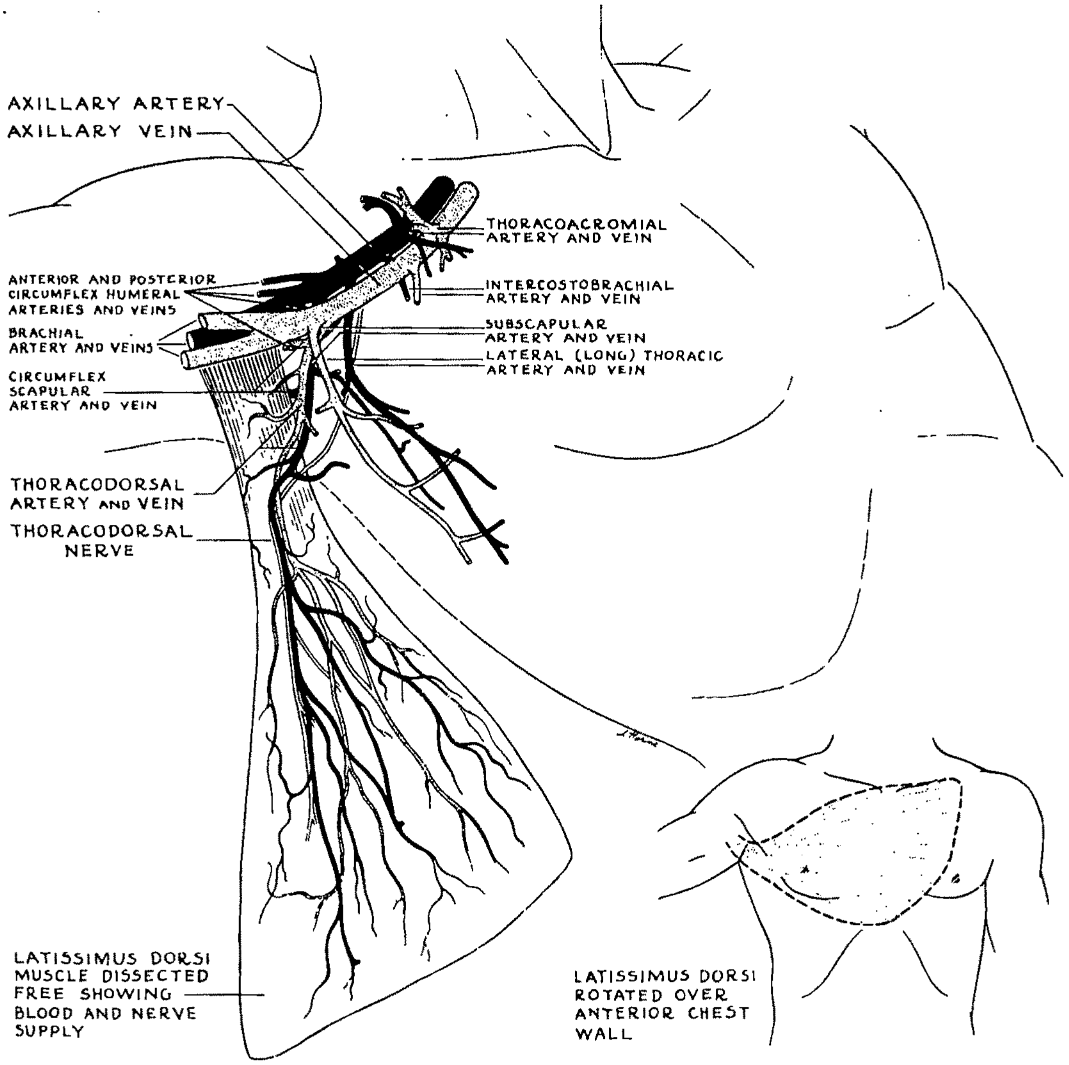
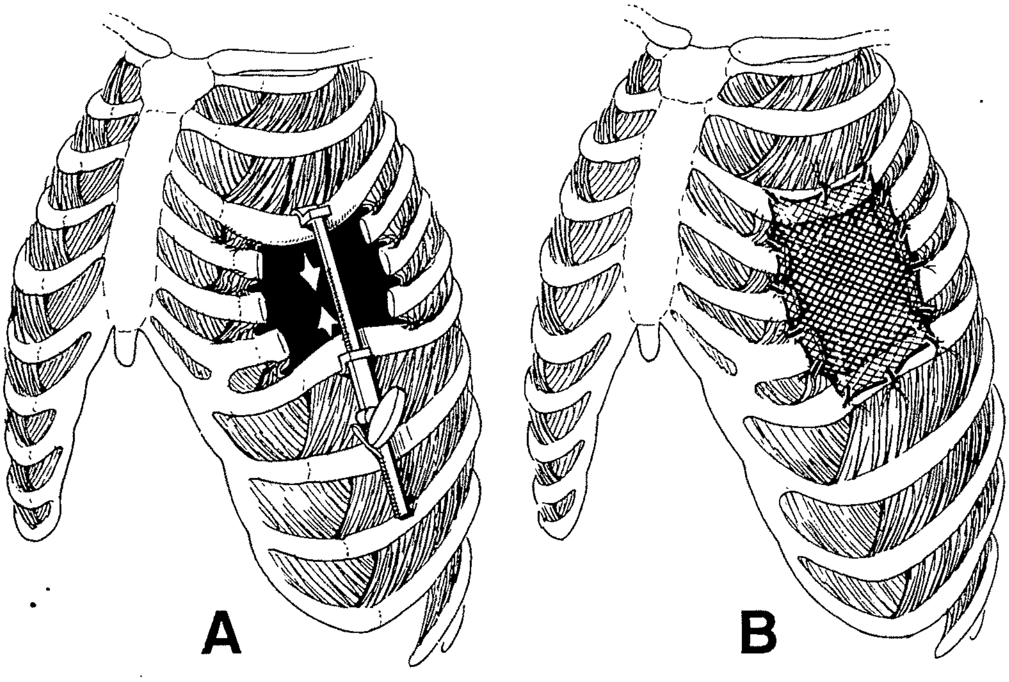

AXILLARY ARTERY
AXILLARY VEIN
THORACOACROMIAL ARTERY AND VEIN
ANTERIOR AND POSTERIOR CIRCUMFLEX HUMERAL ARTERIES AND VEINS
INTERCOSTOBRACHIAL ARTERY AND VEIN
BRACHIAL ARTERY AND VEINS
SUBSCAPULAR ARTERY AND VEIN
LATERAL (LONG) THORACIC ARTERY AND VEIN
CIRCUMFLEX SCAPULAR ARTERY AND VEIN
THORACODORSAL ARTERY AND VEIN
THORACODORSAL NERVE
LATISSIMUS DORSI MUSCLE DISSECTED FREE SHOWING BLOOD AND NERVE SUPPLY
LATISSIMUS DORSI ROTATED OVER ANTERIOR CHEST WALL

FIG. 1. Campbell clearly defined the anatomy of the latissimus dorsi muscle flap in his case report for the reconstruction of a full thickness anterior chest wall defect. (Reprinted with permission from Campbell DA. Reconstruction of the anterior thoracic wall. J Thorac Surg 1950; 19:456–461.)



FIGS. 2A and B. *A*. The placement of the Prolene mesh under tension can be greatly facilitated by securing the mesh to the surrounding thoracic skeleton with the rib approximator in place. *B*. The mesh remains under appreciable tension after the removal of the rib approximator. This helps to maintain structural stability and limit the amount of paradoxical motion after operation.

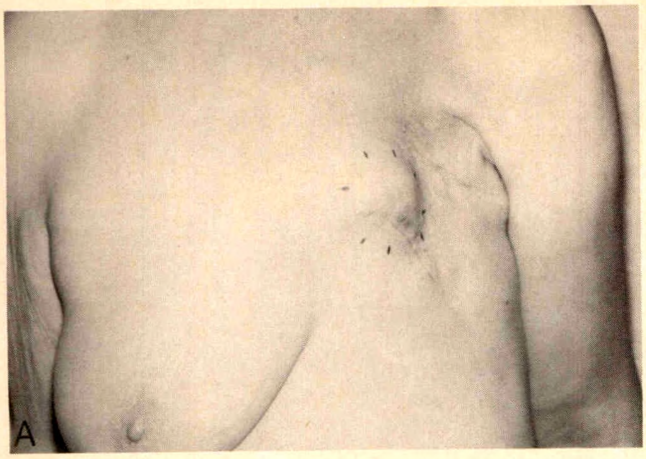


FIG. 3A. This 77-year-old woman presented with a malignant fibrohistiocytoma of the left anterior chest wall. She had had previous radiation for breast cancer.

attention on subtotal sternectomies and advocated only the use of "pectoralis fascia, subcutaneous tissue and skin."

Over the next decade the problems of chest wall reconstruction were continuously examined.[16–18] Chest wall stability continued to be a concern.[19] The use of the omentum in reconstruction was described in 1963 by Kiricuta,[20] and later refined.[21] Although a number of techniques remained in use for chest wall reconstruction, it appeared that the musculocutaneous concept was becoming the most reliable.[22] It was particularly useful after the use of irradiation on the chest wall.[23] The versatility and reliability of the latissimus muscle was

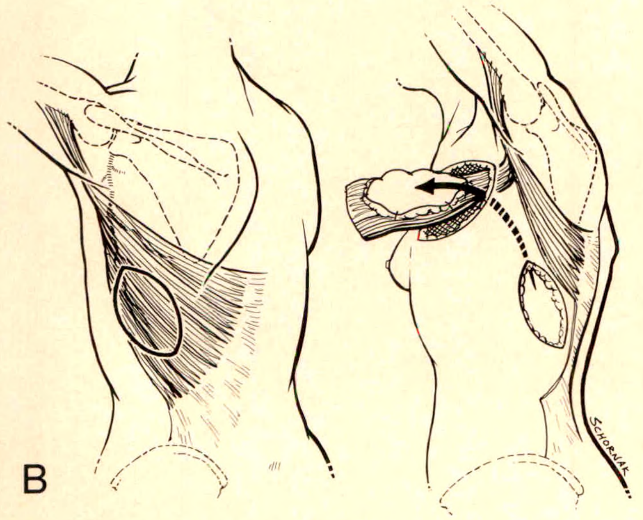


FIG. 3B. A segment of the latissimus dorsi muscle may be selected and transferred with the cutaneous island. This permits a portion of the muscle to remain *in situ* and to continue to function. The reconstructive unit is transferred through the axilla and used on the anterior chest while the donor site may be skin grafted or frequently closed primarily.

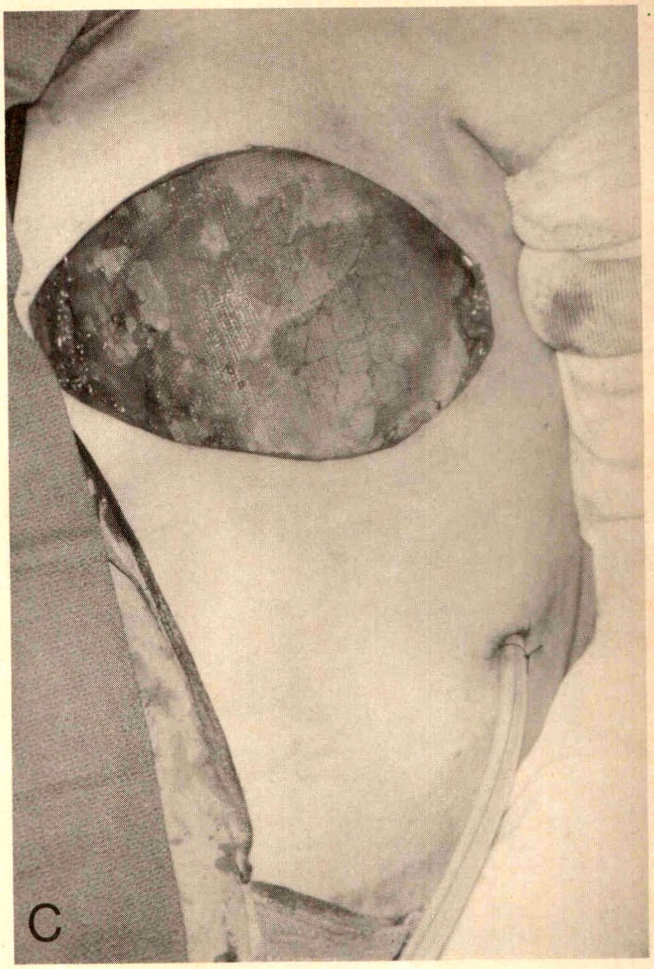


FIG. 3C. The chest wall resection is complete and the Prolene mesh has been placed under tension. The left lung is seen through the Prolene mesh.

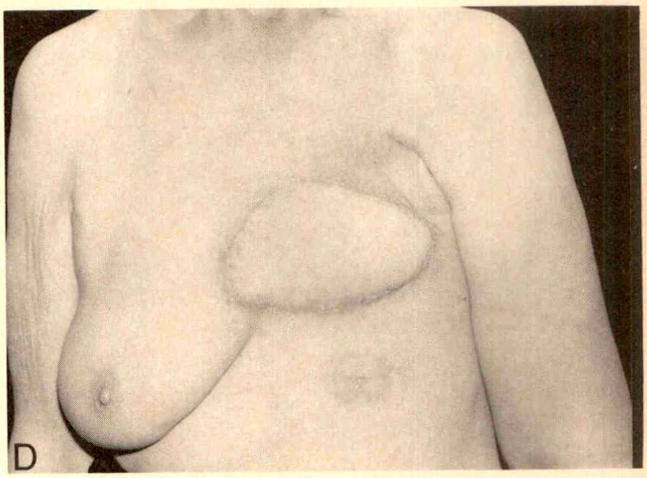


FIG. 3D. Two months after operation the anterior reconstructed chest wound is well healed. A portion of the latissimus muscle remains intact.

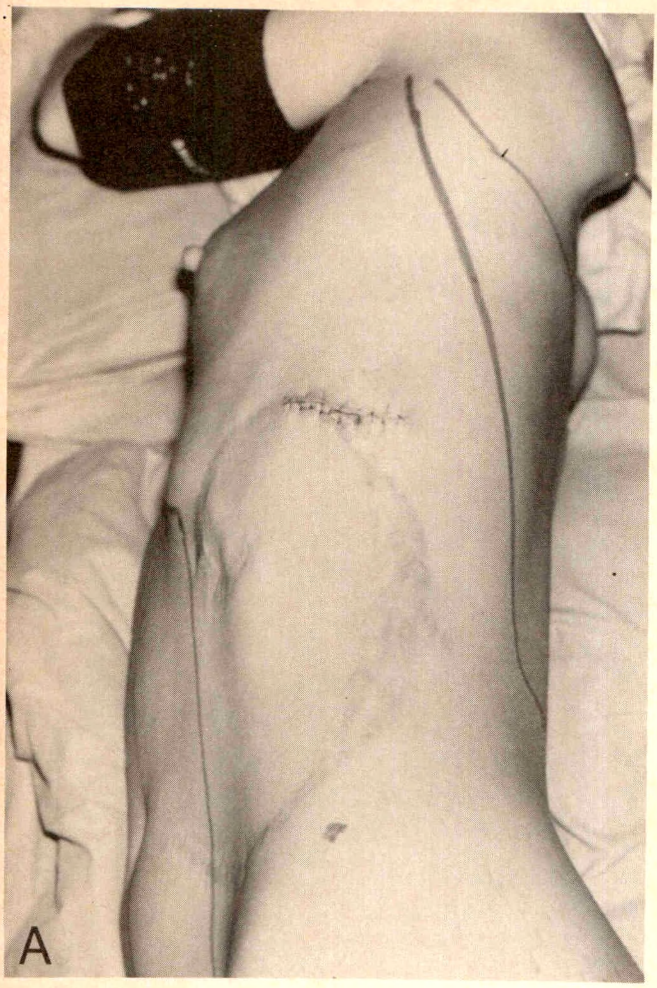


FIG. 4A. This 31-year-old woman presented after the recurrence of a condrosarcoma. The scars from the previous abdominal advancement flap are visible beneath the biopsy site.

reported by Bostwick et al.[24] in a large series of patients. Refinements in the use of musculocutaneous units allowed them to be split into segments.[25] More recently a large series of chest wall reconstructions using a wide variety of techniques was presented with excellent results by Arnold and Pairolero.[26]

Materials and Methods

Between 1982 and 1987 there were 14 consecutive patients at the University of Virginia Medical Center who were treated by full thickness *en bloc* resection of chest wall tumors and immediate reconstruction. The patients were treated jointly by the departments of surgery and plastic surgery. A single method of reconstruction was used in all cases. A latissimus dorsi musculocutaneous flap with fasciocutaneous extensions was used as immediate coverage for the Prolene mesh (Ethicon, Inc., Somerville, NJ) that was used to obtain structural stability of the chest wall.

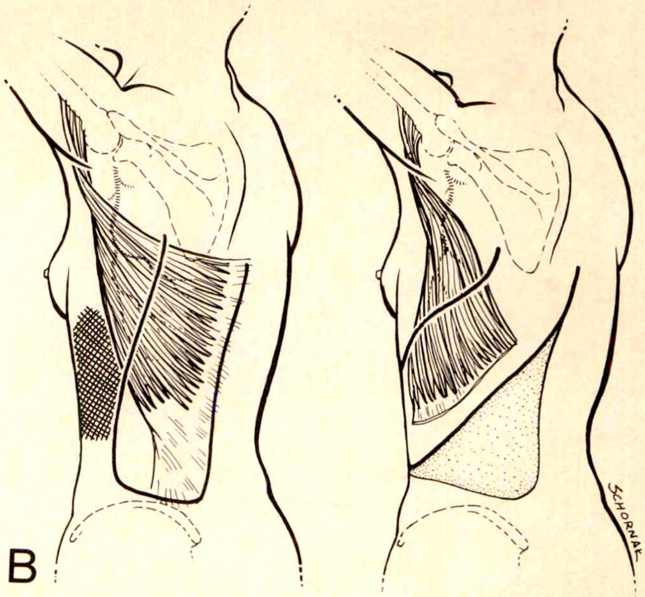


FIG. 4B. The entire latissimus dorsi muscle with an inferior extension to the level of the iliac crest was used to reconstruct this anterior and lateral chest wall defect.

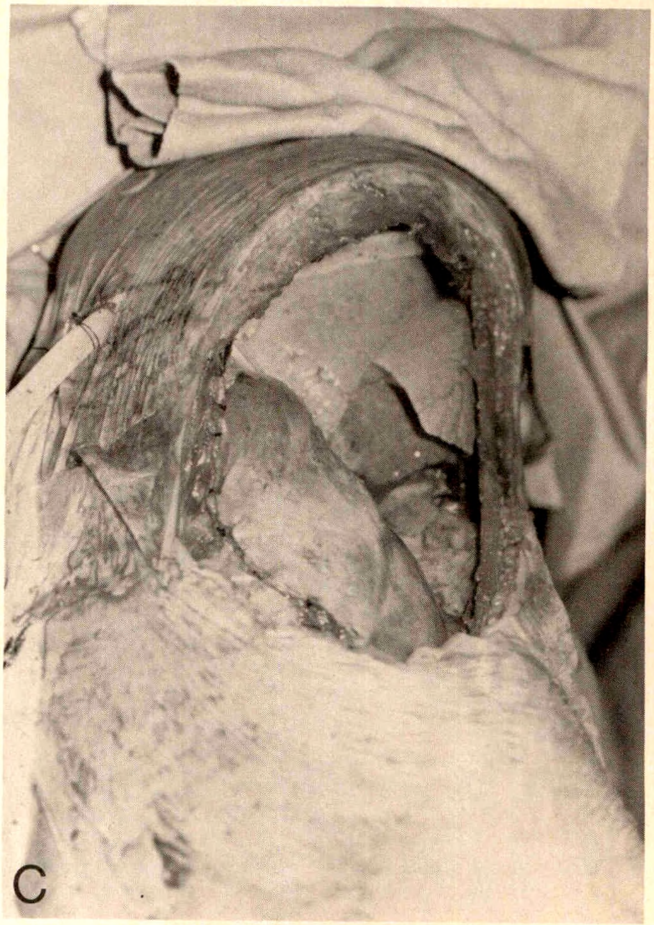


FIG. 4C. The surgical defect created prior to reconstruction reveals the left lung in the upper portion of the defect and the repaired diaphragm in the lower anterior section of the surgical defect.

There were nine females and five males treated. The age range was 31 to 77 years. The mean hospitalization time was 23 days. The pathology of the lesions was varied. They included paraganglioma, malignant schwannoma, malignant fibrous histocytoma, aggressive fibromatosis, radiation necrosis, squamous cell carcinoma (2), fibrosarcoma (2), and breast carcinoma (5). The anatomic location of the defects included anterior (7), lateral (4), and posterior (3). The resection included excision of the bony skeleton in each case. The range of the ribs resected was 2 to 6 with a mean of 3.9 ribs. In three cases the resection included a partial sternectomy in conjunction with the rib resection.

Results

Each of the 14 patients had a single immediate reconstruction with a segmental or total latissimus dorsi musculocutaneous flap. Structural stability was obtained with Prolene mesh. Primary healing was obtained and no secondary procedures were required. All patients were alive at 30 days after operation, and no deaths were attributed to either the resection or the reconstruction. Follow-up study has ranged between 9 and 51 months with a mean of 27.5 months. Successful reoperation for the evaluation of a recurrence was possible in one case 8 months after operation without difficulty. Eleven patients are alive as of this writing.

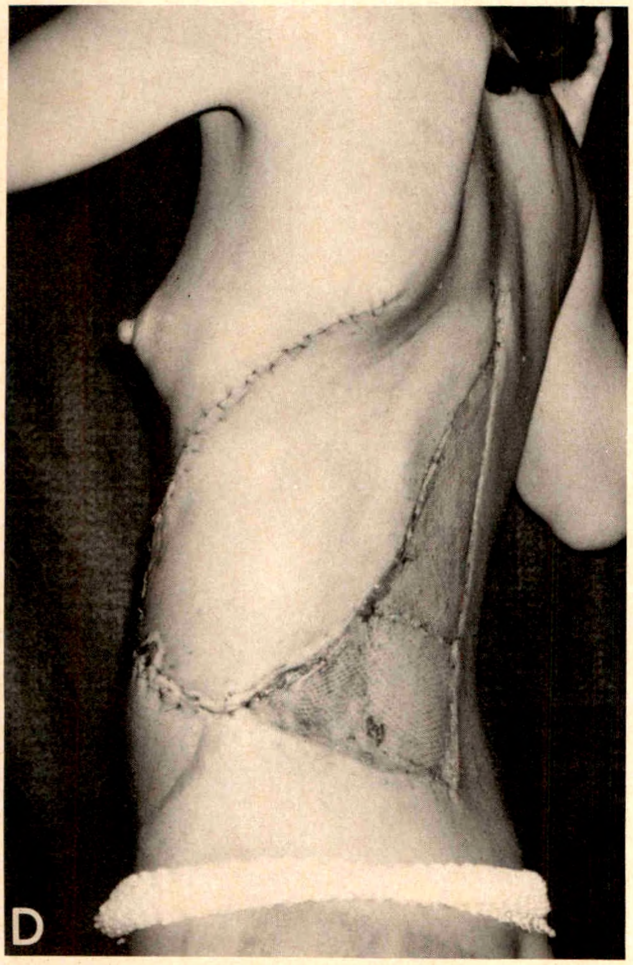


FIG. 4D. One week after operation the musculocutaneous flap is seen and the donor defect has been skin grafted.

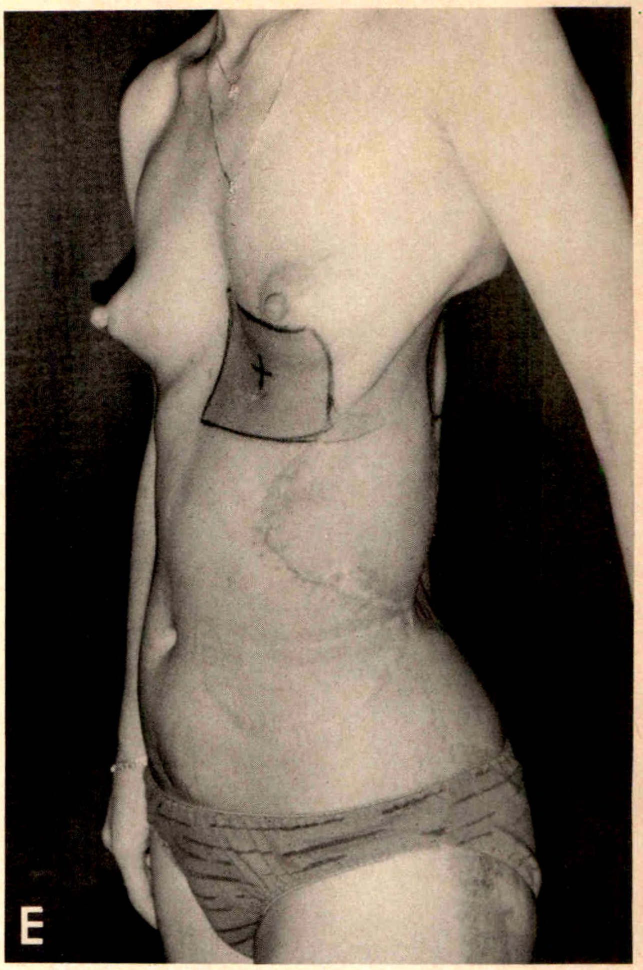


FIG. 4E. The postoperative therapy included irradiation. The anterior port outlined here. The posterior port was designed over the proximal portion of the latissimus dorsi flap. The radiation therapy was tolerated well by the reconstructive musculocutaneous flap.

Functional evaluation was obtained in two patients postoperatively. The Cybex (Cybex, Ronkonkoma, NY) data reduction computer was used and demonstrated that maintaining the correct resting length of the muscle in the transposed position or permitting a segment of innervated muscle to remain *in situ* will preserve a significant amount of total arm adduction power and endurance.

Discussion

This current report confirms the versatility and reliability of the lattissimus dorsi musculocutaneous flap.

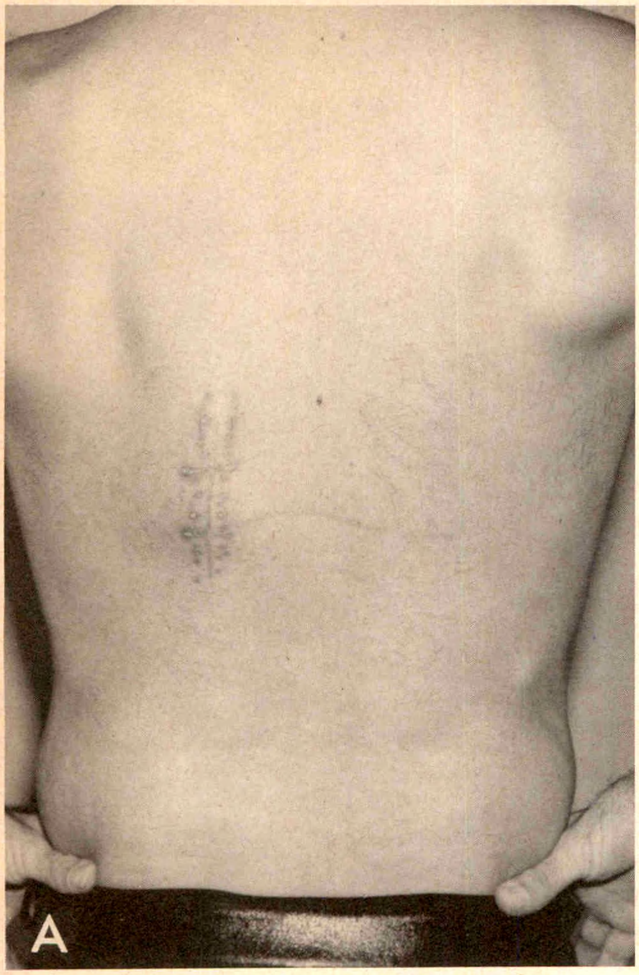


FIG. 5A. This 34-year-old man presented with a biopsy proven aggressive fibromatosis tumor. The left paraspinous location can be seen.

Fasciocutaneous extensions of the flap afford a larger reliable reconstructive unit. Dependable reconstruction allows adequate resection and optimal treatment.

The structural stability of the chest wall can be obtained with the use of Prolene mesh placed under tension. A method used by the authors places the mesh and sutures it firmly in place while the rib approximator remains in position (Fig. 2). When the rib approximator is removed the mesh increases greatly in tension. This greatly reduces the amount of paradoxical motion during spontaneous respiration. Total excision of the sternum was not undertaken in any of the cases presented, and mesh alone may not be adequate in that situation. Prolene mesh has proven to exhibit several desirable characteristics. This surgical mesh is a knitted polypropylene nonabsorbable synthetic. Because the mesh is knitted, it provides for elasticity in both directions. The fiber junctions are interlinked, and, therefore, the mesh is less likely to fracture when flexed as the more rigid metallic mesh are prone to do. The placement of the mesh under appreciable tension is essential in order to obtain structural stability. This polypropylene mesh exhibits not only high tensile strength, but also a high burst strength of approximately 250 lb/in.[2] Previous reports have shown this material to perform well in both reconstruction of the abdominal wall[27] in more than 100 patients and in reconstruction of the chest wall.[26,28]

Anterior upper chest reconstruction may be accomplished with a segmental portion of the muscle (Fig. 3). The superior or inferior portion of the muscle may be transferred with the appropriate amount of subcutaneous tissue for the reconstruction. The portion of the muscle that remains in place continues to function and aid in arm adduction. Cutaneous units of 8–10 cm in width allow primary donor site closure without difficulty.

Surgical defects of the lower anterior chest may require transfer of the entire muscle (Fig. 4). Fasciocutaneous extensions posteriorly to the midline and inferiorly to the level of the iliac crest may be required to resurface

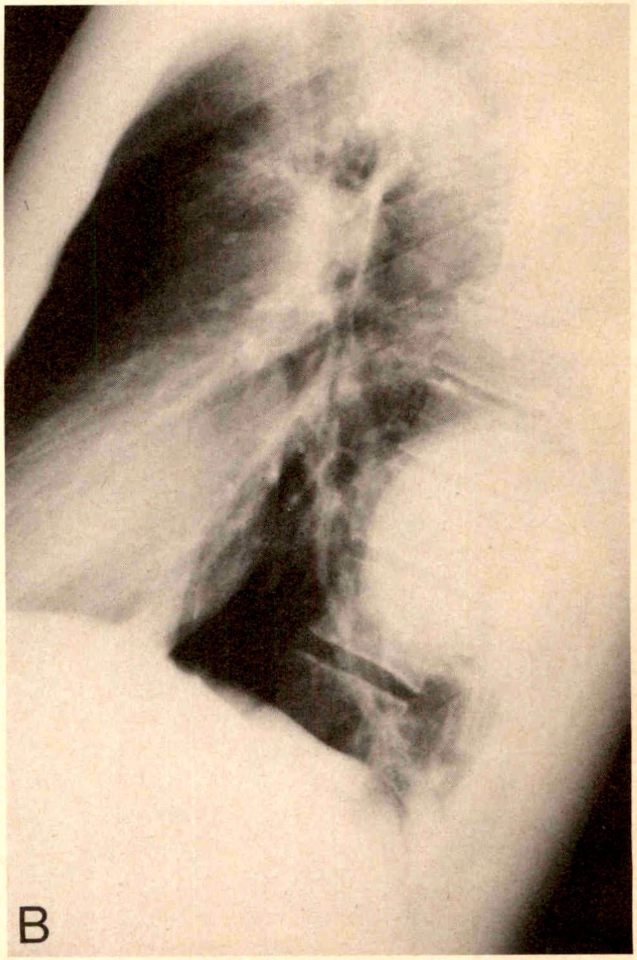


FIG. 5B. The lateral chest roentgenogram shows clearly the intrathoracic extent of the well-circumscribed tumor.

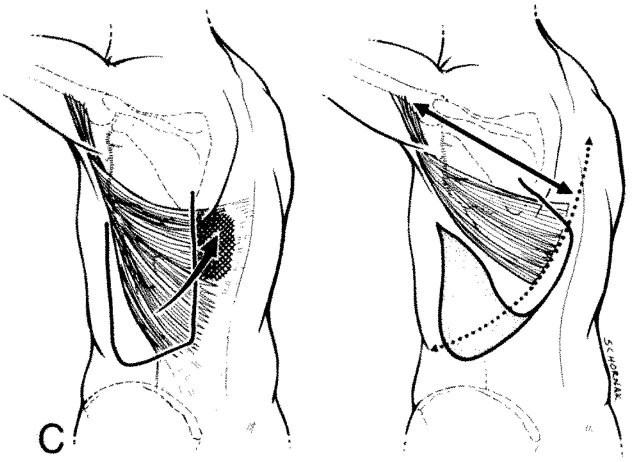


FIG. 5C. The entire origin of the left latissimus muscle was included in the reconstruction. The resting length of the muscle was marked with sutures prior to transfer. The arc of the muscle was drawn on the patient preoperatively and the distal end of the muscle was secured to the surgical defect along that arc. The tension of the muscle was adjusted so that the previously placed sutures were at the same interval after the transfer of the muscle.

the defect. If radiation therapy is contemplated in the postoperative treatment, the location of the ports should be considered. The proposed site for irradiation should be secured with well vascularized tissue. Placement of the transposed muscle in a position that approximates the normal resting length of the innervated muscle can preserve both function of the muscle and the contour of the posterior axillary fold.

Posterior chest wall defects may be reconstructed using the same principles (Fig. 5). Fasciocutaneous extensions inferiorly and anteriorly may be required. If the arc of rotation of the muscle from its insertion on the

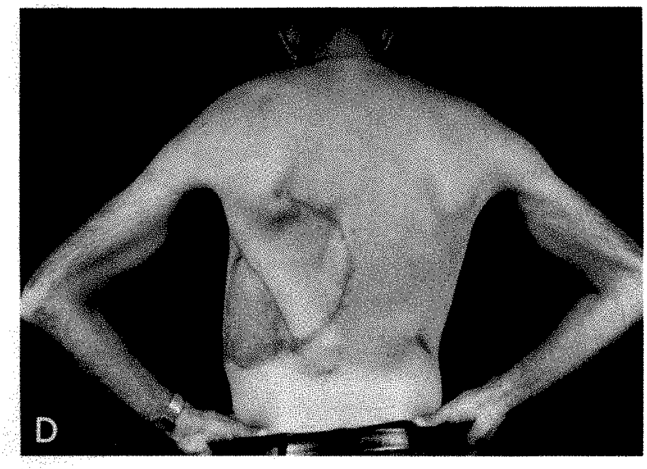


FIG. 5D. After operation the flap is well healed. The arms are in extension with forced adduction, and the preservation of the posterior axillary line by the latissimus muscle can be seen. Postoperative testing confirmed that the function of the muscle remained intact.

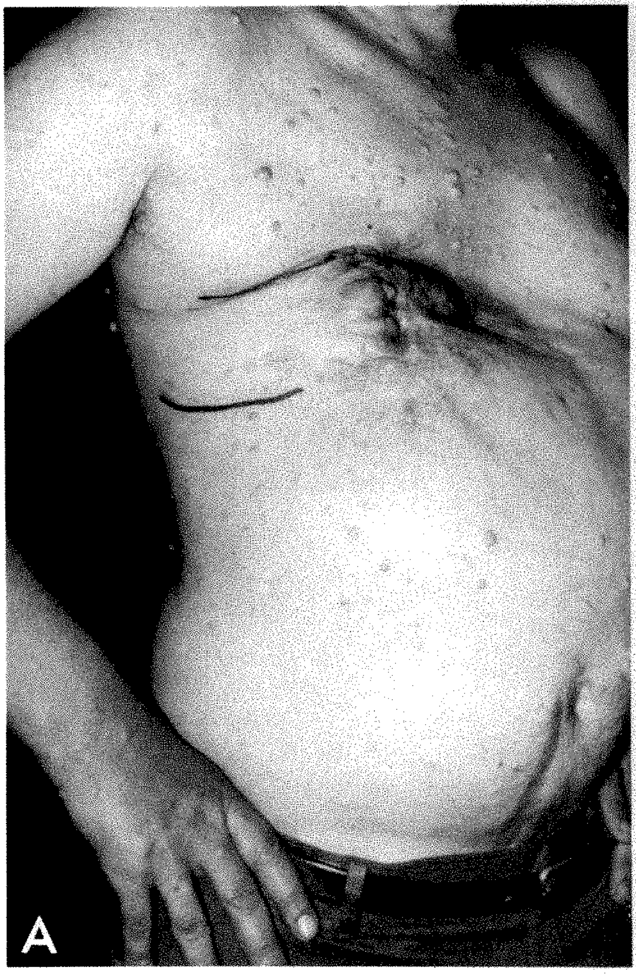


FIG. 6A. This 43-year-old man presented after several unsuccessful attempts at surgical excision of a malignant nerve sheath tumor. The site of the previous surgical scarring on the right chest can be seen at the inferior margin of the pectoralis major muscle.

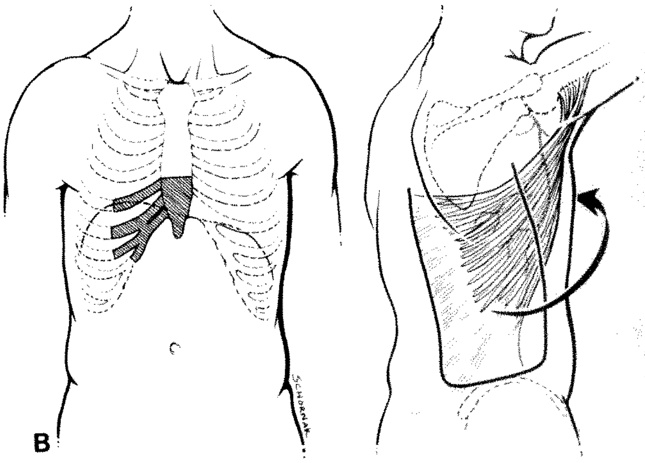


FIG. 6B. The area of resection consists of the inferior third of the sternum as well as the sixth through the ninth ribs. The entire right latissimus muscle with the anterior, inferior, and posterior fasciocutaneous extensions included was transferred to reconstruct the anterior chest defect.

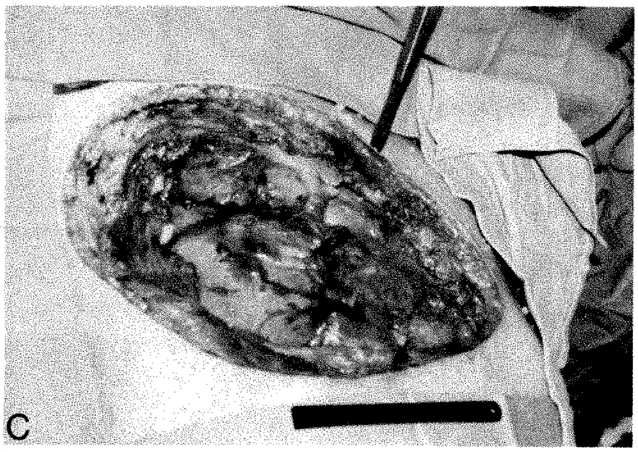


FIG. 6C. The right anterior chest and abdominal defect prior to placement of the mesh.

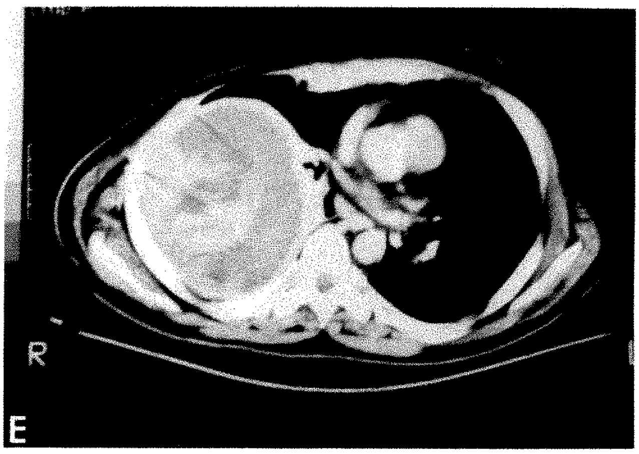


FIG. 6E. Eight months after operation a recurrence of the tumor in the right lower chest was confirmed by CT scan. The tumor can be seen extending into the right thorax.

humerus to its origin is traced, the placement of the muscle in the defect to be reconstructed can be adjusted to maintain the muscle at the appropriate resting length. Prior to transfer the muscle can be marked with sutures at fixed intervals of a few centimeters. Then, when the muscle is relocated the sutures can be readjusted to the appropriate intervals. Preservation of adduction power has been documented as well as the maintenance of the posterior axillary line contour.

Large anterior chest wall defects including a portion of the sternum may also be reconstructed (Fig. 6). The entire ipsilateral latissimus territory, which extends to the midline posteriorly, the middle axillary line anteriorly, and the iliac crest inferiorly, can be used. If a partial sternectomy is included in the skeletal resection, the reconstructive unit may extend across the midline to the contralateral side. If reexploration of the site is necessary for evaluation of a recurrence, the entire musculocutaneous unit can be elevated to allow access to the skeletal defect without difficulty. Uneventful healing can be anticipated.

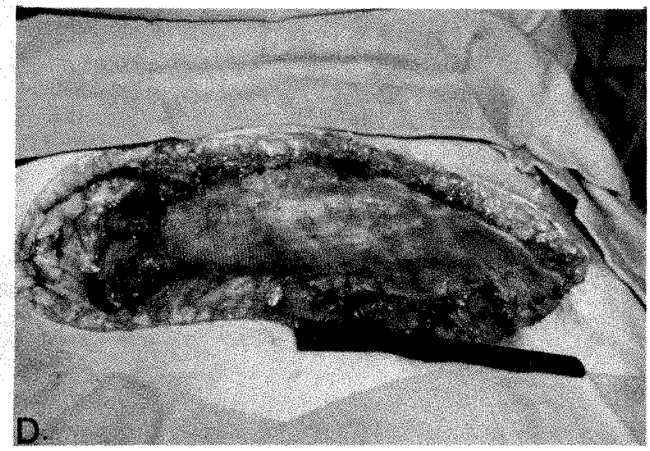


FIG. 6D. After the rib approximator was removed the Prolene mesh remains under tension.

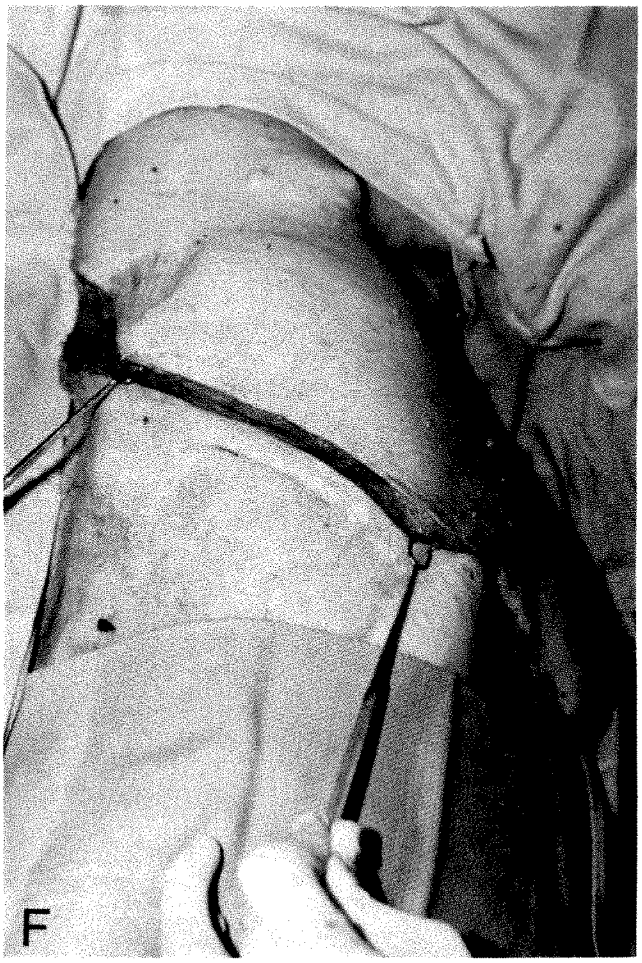


FIG. 6F. Reexploration of the wound was undertaken, and the entire musculocutaneous flap was elevated at its lower margin.

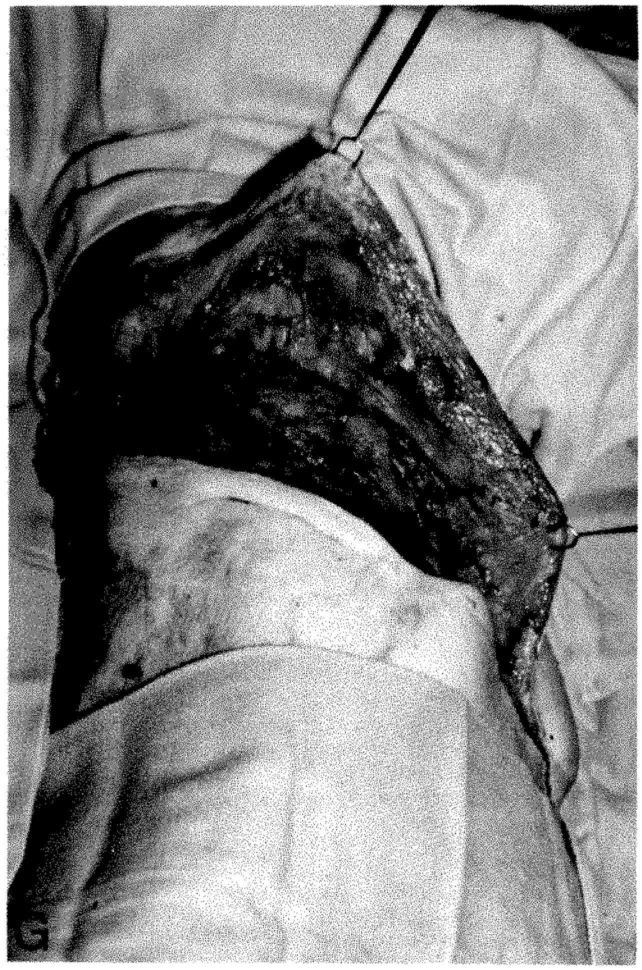


FIG. 6G. The elevation of the flap permitted evaluation both of the right chest as well as the right upper abdomen. Multiple biopsies revealed the tumor to be widely disseminated in the abdominal cavity.

Conclusion

The authors' experience with 14 consecutive patients who had full thickness chest wall excision and primary reconstruction with a single technique, latissimus dorsi musculocutaneous flap with Prolene mesh, is reviewed. The coordinated efforts of the thoracic and plastic surgeons provided optimal care for the patient. Segmental portions of the muscle that are permitted to remain *in situ* or total transfer of the muscle with the correct resting length permit continued documented adduction function of the latissimus dorsi muscle.

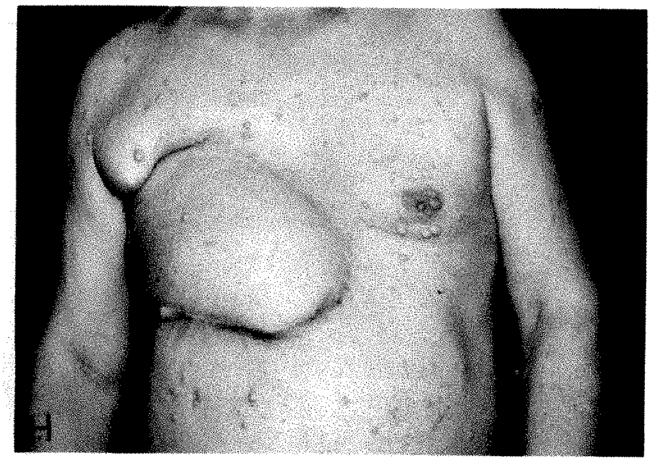


FIG. 6H. After operation the healing was uneventful and the length of the musculocutaneous flap across the midline can be seen.

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DISCUSSION

DR. JOHN J. COLEMAN, III (Atlanta, Georgia): I appreciate the opportunity to participate in this meeting as a guest and to discuss Dr. Morgan's paper.

(Slide) During the last ten years at the Emory University Affiliated Hospitals, we have had the opportunity to deal with a number of complex thoracic defects caused either by trauma, tumor resection, or infected thoracotomy and sternotomy. Our approach has included the latissimus dorsi as an important part of this overall reconstructive plan, but we have developed, by necessity, a slightly different approach for encompassing the possibility of either reoperation secondary to tumor recurrence that might involve the previous reconstruction, or partial or complete failure of the reconstruction effort.

This approach is primarily a Plan A with a Plan B, and occasionally a Plan C, and it has been facilitated by the realization that most of these large flat muscles of the chest wall, either anterior or posterior, have an axial long blood supply, as Dr. Morgan demonstrated, the thoracodorsal pedicle in the latissimus dorsi, and also a segmental blood supply; and in the case of the latissimus, there is the paravertebral perforators of the intercostals.

This is also true of the pectoralis, and, to a lesser degree, the rectus abdominis and the trapezius. The following patient demonstrates this approach:

This is a 44-year-old woman with a three times-recurrent cystosarcoma phylloides, the resection of which required removal of four ribs, repair with Proline, and soft tissue coverage, which was accomplished by a rotation flap of the abdominal wall, based on the perforators from the anterior intercostals.

This approach allowed preservation of the contralateral internal mammary vessels, and also allowed a good repair. Preserving the vessels was, as it turned out, important because about 9 months later, the patient had a large recurrence, as might be suspected with a tumor such as this. This recurrence was addressed by a second resection and transfer of the entire abdominal wall based on the internal mammary vessels.

This approach has been used in ten major anterior chest wall resections, with the inferior epigastric kept in reserve for a possible microvascular anastomosis. So understanding the anatomy in this area allows us considerable flexibility. Our plan has generally been to start with a local musculocutaneous flap and then move, if necessary, to a regional musculocutaneous flap, and finally, to use the omentum or free tissue transfer as a last resort.

I have several questions. First, have you been limited at all by the body habitus of the patient? We have occasionally seen that the latissimus is excellent in a tall, thin patient, but in a short patient or a patient with a large barrel chest, the arc of rotation is limited. What is the safe fasciocutaneous extension of the latissimus flap, and is this limited at all by previous axillary radiation? As you mention in your manuscript, five of the patients had previous breast cancer. We have had some problems with the fasciocutaneous extension of the latissimus, and would appreciate your insight into this.

DR. RALEIGH R. WHITE (Temple, Texas): I think the authors of this paper are to be greatly congratulated. It is a pleasure and a true benefit for me to see a paper that will help me directly in my practice when I return home. I truly appreciate the wonderful demonstration of that extended flap.

I rise to ask one specific question regarding the material that we have been using recently to repair these larger defects with a more solid material, Gortex sheeting.

It seemed good to isolate the abdominal and the thoracic cavities in these larger defects with a more solid piece of material rather than porous mesh. I wonder if you have any recent experience with that and if you would have any advice for us on its use.

DR. P. G. ARNOLD (Rochester, Minnesota): I congratulate the authors on a paper that is both well presented and well written. I also appreciate having the chance to review it earlier.

In my own practice, I am in a special situation working with Dr. Peter Pairolero, who is a busy thoracic and vascular surgeon. We do a great deal of work together.

During the last ten years, we have had the opportunity to work together on about 152 of these chest wall tumors. In a third of this group we simply took the tumor out and closed the skin again after dealing with the skeletal defect.

In the 112 that were closed with muscle flaps, half of these were latissimus dorsi muscle. (In seven instances we used another muscle in addition to the latissimus dorsi muscle). Primarily we used the pectoralis muscle or another local muscle in the other half. We used a mesh if, in 84 patients, it was a clean wound (Prolene was used in 53 patients and Gortex in 32). Gortex is nice when you need a watertight closure. It costs more, but they both have advantages.

My question to Dr. Morgan is: Is the latissimus dorsi muscle flap your first choice for a chest wall reconstruction, regardless of where the tumor is located? If it is an anterior tumor, is that still your first choice?

I realize that, geometrically speaking, as long as the axis and arc is present, we can move muscles and skin from any part of the chest to any other part of the chest. Do you have a "recipe" that you go through in your own mind in deciding what to use in your reconstruction? Obviously, this presentation is about just one particular muscle flap, and I would be interested in what your other options were, and if for some reason they failed as a flap.

DR. WILLIAM D. SPOTNITZ (Closing discussion). I would like to thank the discussants for their excellent questions and Dr. Morgan for the opportunity of closing this paper at the 100th anniversary meeting of the Southern Surgical Association.

In response to Dr. White's question, we have not had a great deal of experience with Gortex, but we have read of its use and agree with Dr. Arnold that it is a very pliable, good material. It certainly restricts the flow of air and fluid, although it is semipermeable, and it would be the material of choice if one were trying to perform a diaphragmatic repair.

In response to Dr. Coleman, we agree that the patient's body habitus needs to be considered in the choice of this type of flap, and we agree that patients who are excessively obese and short or barrel chested may require additional consideration in use of the latissimus dorsi flap.

We have not had experience in using this flap in patients who have had axillary irradiation. As illustrated by Dr. Morgan, we have used this flap in patients who needed postoperative radiotherapy, and when the ports were specifically designed to take into account the use of the muscle flap, those patients have not had problems. However, I can't comment on those patients who have had preoperative irradiation to the axilla.

We agree with Dr. Arnold that patients who have limited rib resections on the order of 1 to 2 ribs can certainly have their skin closed and don't need these dramatic, beautiful flaps that Dr. Morgan has shown.

In closing I would like to comment that in terms of our choice of flaps, we do agree that with small anterior defects high up on the chest, we would attempt to use pectoralis major flaps first, and that inferiorly we might very well use rectus abdominus flaps. Also, as Dr. Arnold has previously recommended, we keep the omentum as an alternative and secondary means of closing defects that are not successfully treated with musculocutaneous flaps.

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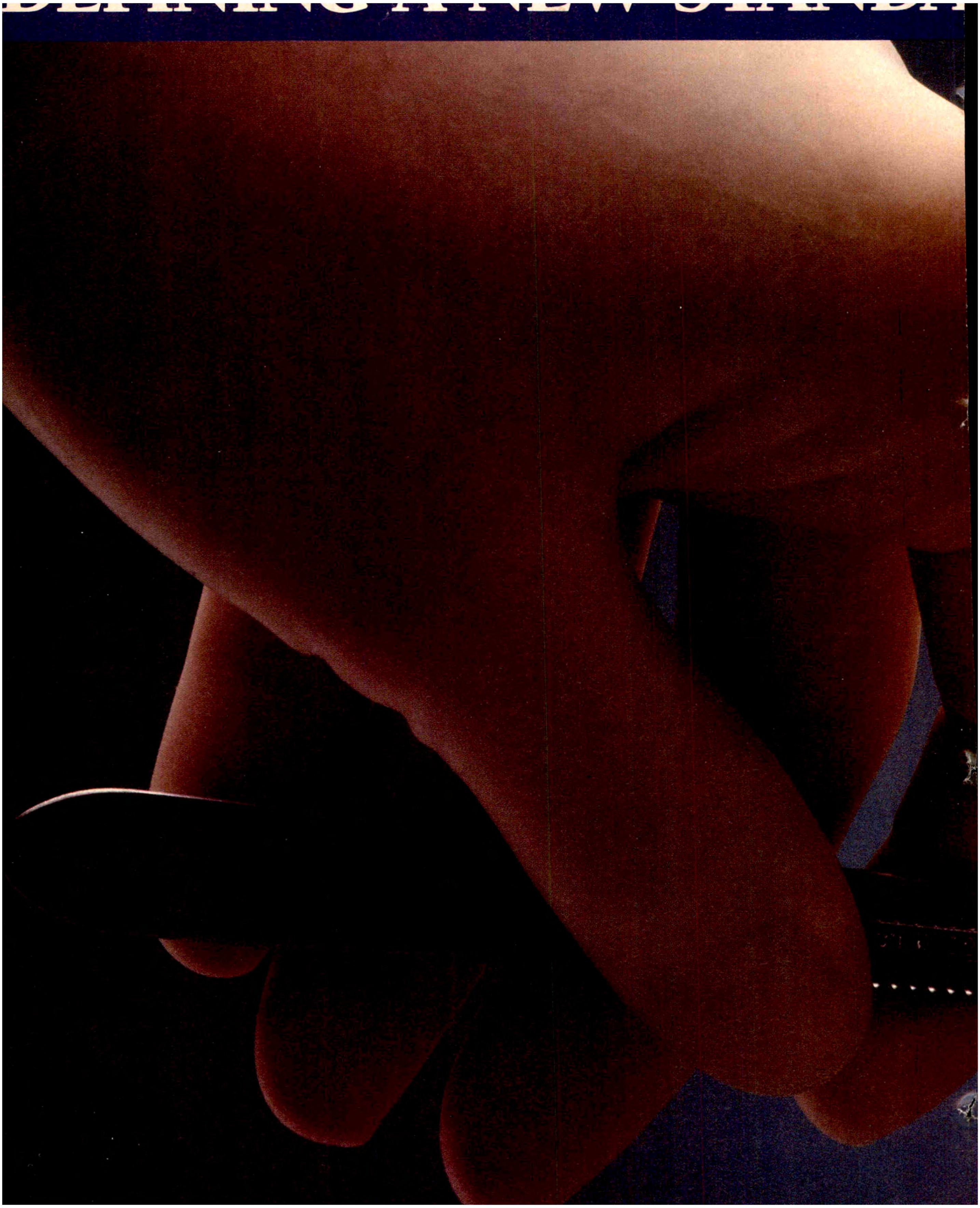
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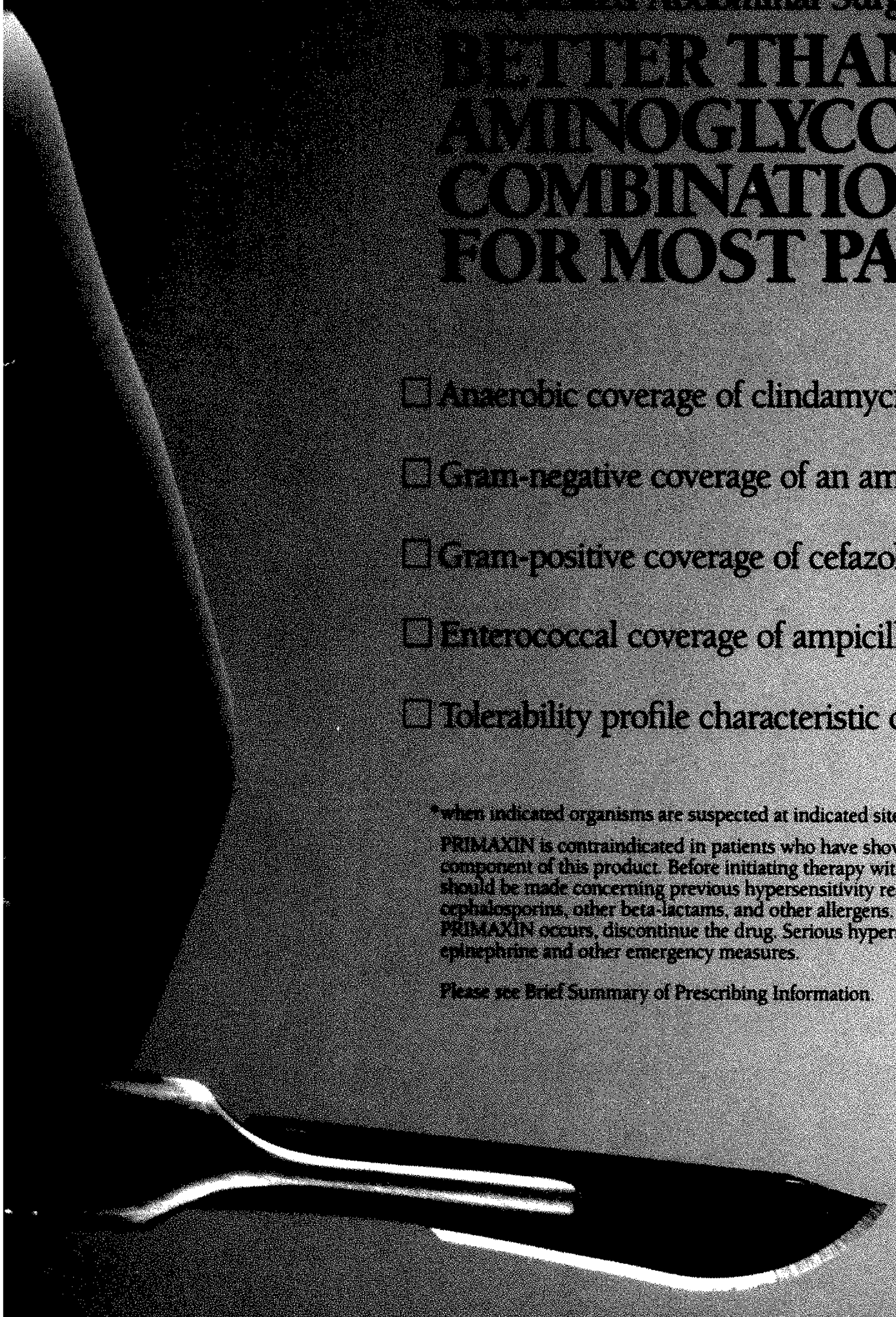

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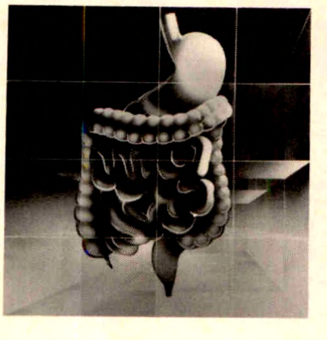

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Pseudomembranous colitis has been reported with virtually all antibiotics, including PRIMAXIN; therefore it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. This colitis may range in severity from mild to life threatening.

Mild cases of pseudomembranous colitis may respond to drug discontinuance alone. In more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte, and protein supplementation, and the use of a drug such as oral vancomycin, as indicated. Isolation of the patient may be advisable. Other causes of colitis should also be considered.

Precautions: *General*—CNS adverse experiences such as confusional states, myoclonic activity, and seizures have been reported during treatment with PRIMAXIN, especially when recommended dosages were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. However, there have been reports of CNS adverse experiences in patients who had no recognized or documented underlying CNS disorder or compromised renal function.

Patients with severe or marked impairment of renal function, whether or not undergoing hemodialysis, had a higher risk of seizure activity when receiving maximum recommended doses than those with no impairment of renal function; therefore, maximum recommended doses should be used only where clearly indicated (see DOSAGE AND ADMINISTRATION).

Patients with creatinine clearances of ≤5 mL/min/1.73 m² should not receive PRIMAXIN unless hemodialysis is instituted within 48 hours.

For patients on hemodialysis, PRIMAXIN is recommended only when the benefit outweighs the potential risk of seizures.

Close adherence to the recommended dosage and dosage schedules is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of PRIMAXIN re-examined to determine whether it should be decreased or the antibiotic discontinued.

As with other antibiotics, prolonged use of PRIMAXIN may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken. While PRIMAXIN possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system function during prolonged therapy is advisable.

Drug Interactions—Since concomitant administration of PRIMAXIN and probenecid results in only minimal increases in plasma levels of imipenem and plasma half-life, it is not recommended that probenecid be given with PRIMAXIN.

PRIMAXIN should not be mixed with or physically added to other antibiotics. However, PRIMAXIN may be administered concomitantly with other antibiotics, such as aminoglycosides.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Gene toxicity studies were performed in a variety of bacterial and mammalian tests *in vivo* and *in vitro*. The tests were: V79 mammalian cell mutation assay (PRIMAXIN alone and imipenem alone), Ames test (cilastatin sodium alone), unscheduled DNA synthesis assay (PRIMAXIN), and *in vivo* mouse cytogenicity test (PRIMAXIN). None of these tests showed any evidence of genetic damage.

Reproduction tests in male and female rats were performed with PRIMAXIN at dosage levels up to 8 times the usual human dose. Slight decreases in live fetal body weight were restricted to the highest dosage level. No other adverse effects were observed on fertility, reproductive performance, fetal viability, growth, or postnatal development of pups. Similarly, no adverse effects on the fetus or on lactation were observed when PRIMAXIN was administered to rats late in gestation.

Pregnancy—Pregnancy Category C: Teratogenicity studies with cilastatin sodium in rabbits and rats at 10 and 33 times the usual human dose, respectively, showed no evidence of adverse effect on the fetus. No evidence of teratogenicity or adverse effect on postnatal growth or behavior was observed in rats given imipenem at dosage levels up to 30 times the usual human dose. Similarly, no evidence of adverse effect on the fetus was observed in teratology studies in rabbits with imipenem at dosage levels at the usual human dose.

Teratology studies with PRIMAXIN at doses up to 11 times the usual human dose in pregnant mice and rats during the period of major organogenesis revealed no evidence of teratogenicity.

Data from preliminary studies suggest an apparent intolerance to PRIMAXIN (including emesis, inappetence, body weight loss, diarrhea, and death) at doses equivalent to the average human dose in pregnant rabbits and cynomolgus monkeys that is not seen in nonpregnant animals in these or other species. In other studies, PRIMAXIN was well tolerated in equivalent or higher doses (up to 11 times the average human dose) in pregnant rats and mice. Further studies are under way to evaluate these findings.

There are, however, no adequate and well-controlled studies in pregnant women. PRIMAXIN should be used only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRIMAXIN is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in infants and children below 12 years of age have not yet been established.

Adverse Reactions: PRIMAXIN is generally well tolerated. Many of the 1,723 patients treated in clinical trials were severely ill and had multiple background diseases and physiological impairments, making it difficult to determine causal relationship of adverse experiences to therapy with PRIMAXIN.

Local Adverse Reactions—Local adverse clinical reactions that were reported as possibly, probably, or definitely related to therapy with PRIMAXIN were: phlebitis/thrombophlebitis (3.1%), pain at the injection site (0.7%), erythema at the injection site (0.4%), vein induration (0.2%), infused vein infection (0.1%).

Systemic Adverse Reactions—The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to PRIMAXIN were: nausea (2.0%), diarrhea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%) (see PRECAUTIONS), dizziness (0.3%), pruritus (0.3%), urticaria (0.2%), somnolence (0.2%).

Additional adverse systemic clinical reactions reported as possibly, probably, or definitely drug related occurring in less than 0.2% of the patients or reported since the drug was marketed are listed within each body system in order of decreasing severity: *Gastrointestinal*—pseudomembranous colitis (see WARNINGS), hemorrhagic colitis, gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, heartburn, pharyngeal pain, increased salivation; *CNS*—encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, psychic disturbances; *Special Senses*—transient hearing loss in patients with impaired hearing, tinnitus; *Respiratory*—chest discomfort, dyspnea, hyperventilation, thoracic spine pain; *Cardiovascular*—palpitations, tachycardia; *Renal*—oliguria/anuria, polyuria; *Skin*—erythema multiforme, facial edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae; *Body as a Whole*—polyarthralgia, asthenia/weakness.

Adverse Laboratory Changes—Adverse laboratory changes without regard to drug relationship that were reported during clinical trials or reported since the drug was marketed were: *Hepatic*—increased SGPT, SGOT, alkaline phosphatase, bilirubin, and LDH; *Hemic*—increased eosinophils, positive Coombs test, decreased WBC and neutrophils, including agranulocytosis, increased WBC, increased platelets, decreased platelets, decreased hemoglobin and hematocrit, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils; *Electrolytes*—decreased serum sodium, increased potassium, increased chloride; *Renal*—increased BUN, creatinine; *Urinalysis*—presence of urine protein, urine red blood cells, urine white blood cells, urine casts, urine bilirubin, and urine urobilinogen.

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WILLIAM D. SUGGS, M.D., HORACE F. HENRIQUES, M.D., and RALPH G. DEPALMA, M.D.

From the Department of Surgery, George Washington University Medical Center, Washington, D.C.

This study sought to minimize juxta-anastomotic neointimal hyperplasia (JNIH) following the use of polytetrafluoroethylene (PTFE) conduits. PTFE anastomoses to canine carotid arteries (noncuff grafts) were compared with grafts with vein cuffs interposed proximally and distally between the graft and native artery. This technique has been suggested clinically for below-knee PTFE femoropopliteal reconstruction. Twelve dogs received aspirin for 1 week before operation, which was continued after each animal received bilateral cuff and noncuff 4-mm PTFE grafts. At sacrifice, after 3–12 weeks, graft patency was assessed and luminal diameters measured with ophthalmic calipers at three sites along the anastomoses and 1 mm proximal or distal to graft toe (A′ diameter). Specimens were perfusion fixed at arterial pressure for gross and histologic study; selected arteries were additionally fixed with 4% buffered glutaraldehyde, stored at 4 C, and examined immunochemically using antimyosin antibody immunopurified for smooth muscle. Overall patency of noncuff grafts in 11 long-term surviving dogs was 4 of 11; patency of the cuff grafts was 7 of 11. Regardless of graft thrombosis, antibody positive cellular proliferation occurred mainly at noncuffed PTFE anastomoses. Luminal encroachment was predominantly due to subintimal proliferation of cells highly reactive to smooth muscle derived antibody. JNIH was most prominent 1 mm distal to the graft toe (A′ distal diameter). Average A′ for noncuff grafts was 1.82 mm ± 0.97 SEM; average A′ diameter for cuff grafts was 3.41 mm ± 0.74 SEM ($p < 0.001$). Vein cuff inhibition of proliferation of smooth muscle or cells derived from smooth muscle possibly relates to wider distribution of kinetic energy (less compliance mismatch) or to interposition of venous endothelium.

AN IMPORTANT CAUSE of arterial prosthetic failure is the development of neointimal fibrous proliferation.[1] This process causes stenoses commonly located just proximal and distal to the graft–artery anastomosis in juxta-anastomotic locations. Juxta-anastomotic neointimal hyperplasia (JNIH) causes reduction of flow and subsequent graft failure. The cellular and mechanical factors promoting JNIH are still incompletely understood. Hemodynamic factors,[1,2] graft–artery compliance mismatch,[3] chronic endothelial injury,[4] and pannus ingrowth[5] have all been implicated.

JNIH is common to all types of grafts; however, it has been particularly troublesome with small caliber polytetrafluorethylene (PTFE) grafts. Miller et al.[6] proposed using an interposition vein cuff at the distal anastomosis of PTFE grafts to infrageniculate arteries. The senior author (RDP) has also used vein cuffed anastomoses to PTFE in limb salvage procedures to replace failed vein grafts. Patencies were somewhat longer than might be expected.

This study tested the hypothesis that interposition vein cuffs might prevent JNIH and improve patency of small caliber PTFE grafts. An experimental model was developed to compare vein cuff interposition with standard end-to-side bypass. Stenoses due to JNIH were quantitated; JNIH was mainly due to proliferation of smooth muscle or cells derived from smooth muscle. Moreover, vein cuff interposition between small caliber PTFE grafts and indigenous artery inhibited JNIH.

Materials and Methods

Twelve mongrel dogs weighing 20–25 kg of both sexes (8 males, 4 females) were used. Subjects were treated according to *The Guide for Care and Use of Laboratory Animals,* NIH Publication 8523, 1985. After a period of conditioning and quarantine, all dogs were given 325 mg of aspirin by mouth daily for 7 days before surgery. Aspirin administration was continued after operation until the animals were killed at intervals from 3 weeks to

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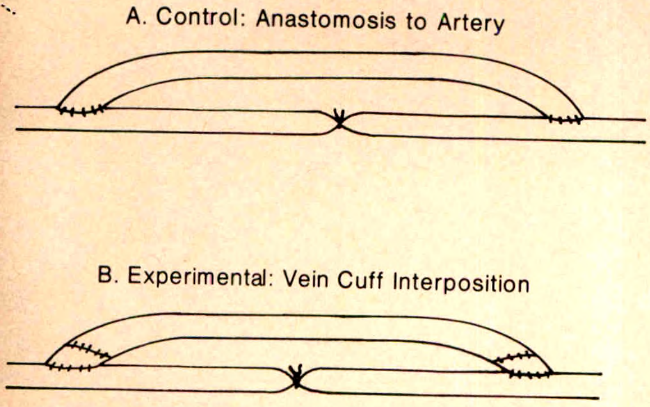

A. Control: Anastomosis to Artery
B. Experimental: Vein Cuff Interposition

FIGS. 1A and B. *A*. Control: PTFE to artery anastomoses. *B*. Experimental: interposition of vein cuff.

12 weeks. Before operation, the dogs received cefazolin (Eli Lilly and Co., Indianapolis, IN) 500 mg intravenously and 500 mg intramuscularly for 5 days after operation. The dogs were initially anesthetized with Biotal®, 20 mg/kg intravenously (Boeringer Ingelheim Animal Health Inc., St. Joseph, MO) and endotracheal intubation was carried out.

Under nitrous oxide and fluoroethylene anesthesia, bilateral neck incisions were made. Both common carotid arteries were dissected for a length of 10 cm. Heparin, 50 units/kg body weight, was administered intravenously. The external jugular vein was dissected and two 6-mm portions of this vein were harvested without distention or irrigation for use as interposition vein cuffs.

On one side, as a control, a 6-cm length of externally supported lightweight 4-mm PTFE graft (GORE-TEX®) was anastomosed in an end-to-side fashion. This artery was then ligated in its center portion. On the opposite side, a vein cuff test site, 6-mm beveled vein cuffs were anastomosed to the indigenous artery in an end-to-side fashion. A 6-cm length of externally supported PTFE was then anastomosed end-to-end to the proximal and distal vein cuffs and the artery similarly ligated. All anastomoses were performed with continuous sutures of 7-0 polytetrafluorethylene using loupe magnification. Graft insertion angles approximated 30° and the anastomoses measured 1–1.3 cm in length. Figure 1 shows the model diagrammatically.

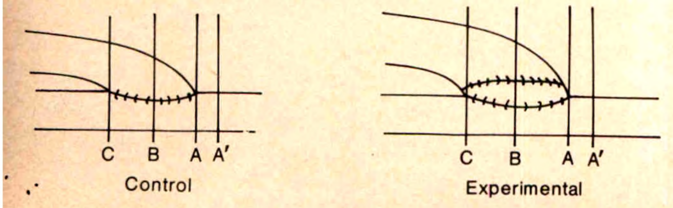


FIG. 2. Cross-sections of anastomotic diameters for measurement and histologic examination. Section A′, shown here in a distal anastomosis, was always taken 1 mm from toe of graft.

The patency of the noncuffed and cuffed grafts was compared in individual animals and among the entire group using selected anastomotic diameters. To obtain arterial diameters approximating those occurring *in vivo* arteries were perfusion fixed at an arterial pressure of 100 mmHg using 2.5% buffered glutaraldehyde (Electron Microscopy Sciences, Fort Washington, PA). Arterial specimens were then resected for luminal measurement, histologic, and immunohistochemical examinations. Ophthalmic calipers were used to measure the luminal diameters of each section. Figure 2 shows details of the anastomotic configuration of the cuffed and noncuffed grafts and the cross-sectional diameters measured. The following graft–arterial sections were obtained: (1) A′—1 mm distal or proximal from the toe of the anastomosis; (2) A—the toe of the anastomosis; (3) B—midportion of the anastomosis; (4) C—heel of the anastomosis.

Eleven dogs were killed by initiating general anesthesia and perfusing the carotid arteries with glutaraldehyde solution. These procedures were used on all dogs except for one animal dying of a stroke within 24 hours of operation. At postmortem examination the stroke in this animal was found to be due to acute thrombosis of the noncuffed carotid graft side. Measurements from this subject were not used in further analyses. No other strokes occurred. The measurements of luminal diameters were averaged and compared for significant differences using Student's t-test.[7] Just before sacrifice and after perfusion, each grafted arterial segment was examined for patency; the incidence of graft patency to graft closure in the two groups was also compared.

Proximal and distal arterial rings comprising A′, A, B, and C diameters were sectioned and examined microscopically after staining with hematoxylin and eosin. In addition, cuffed and noncuffed arterial specimens from two dogs were fixed in 4% glutaraldehyde, frozen at −70 C, and fixed in OCT compound (Miles Scientific, Napeville, IL). These frozen sections were cut in 8-μm thicknesses and stained with antimyosin antibody purified using immunoaffinity chromatography for smooth muscle myosin (Technicon Instruments Corp., Glendale, CA). Immunofluorescent antibody staining was performed using the methodology described in the Kalstead Fluorescence Autoantibody Manual.[8]

Results

The most severe juxta-anastomotic neointimal hyperplasia occurred at the A and A′ segments. The degree of stenosis caused by neointimal hyperplasia was most prominent in the proximal and distal segments of noncuffed PTFE to artery anastomoses and was most severe at distal anastomoses. Table 1 compares mean diameters of proximal and distal A and A′ sites. Stenoses secondary to JNIH were quantitatively most significant at the proximal A ($p < 0.002$) and distal A′ ($p < 0.001$) cross-sectional areas of the noncuffed grafts. The remaining segments B and C were not found to exhibit statistically significant differences in lumen diameters either proximally or distally.

The immunochemical and histologic examinations showed this process mainly to be due to proliferation of smooth muscle or cells derived from smooth muscle. Little or no reactivity to smooth muscle-derived myosin occurred at the junction of the PTFE to the beveled vein cuffs. Figure 3 demonstrates intense reactivity to smooth muscle-derived myosin at noncuff PTFE artery anastomoses, whereas at the vein cuff–PTFE anastomoses (Fig. 4), cellular proliferation is scanty. Figure 5 shows typical juxta-anastomotic neointimal hyperplasia at the distal A′ segment.

Table 2 shows comparative patencies over time in each animal. The vein cuff grafts were open more frequently; however, this difference cannot be considered statistically in a sample this size with individual variations in thrombogenicity, which will be later considered. Examination of the grafts and correlation with the degree of intimal stenosis demonstrated that graft closure and the process of neointimal hyperplasia were sometimes nonconcordant. Graft thrombosis occurred despite antiplatelet therapy, and on three occasions occurred in the absence of demonstrable stenoses due to neointimal hyperplasia.

TABLE 1. *Average Juxta-Anastomotic Diameters (mm) ± SEM (N = 11)*

	Proximal A	Distal A
Cuff	3.81 ± 1.16	3.18 ± 1.04
SE difference	0.50 $p < 0.002$	0.45 $p < 0.069$
Noncuff	1.73 ± 1.19	2.27 ± 1.50
	Proximal A′	Distal A′
Cuff	3.09 ± 0.74	3.41 ± 0.74
SE difference	0.47 $p < 0.053$	0.34 $p < 0.001$
Noncuff	2.10 ± 1.27	1.82 ± 0.97

Discussion

Vein cuff interposition between PTFE and native artery clearly inhibited JNIH. Moreover, JNIH was mainly due to proliferation of smooth muscle or cells derived from smooth muscle as demonstrated by immunohistochemical reactivity. It is probable that vein cuff interposition tended to minimize unfavorable hemodynamic forces promoting neointimal proliferation, as suggested by Imparato et al.[1] over a decade and a half ago and later by LoGerfo et al.[9] The current observations support the thesis that hemodynamic factors promote JNIH at stereotypic sites just proximal or distal to arterial graft anastomoses, *i.e.*, at the A and A′ sections just at the toe or just distal to the toe of the grafts.[10] Clinically, neointimal hyperplasia is also seen at these

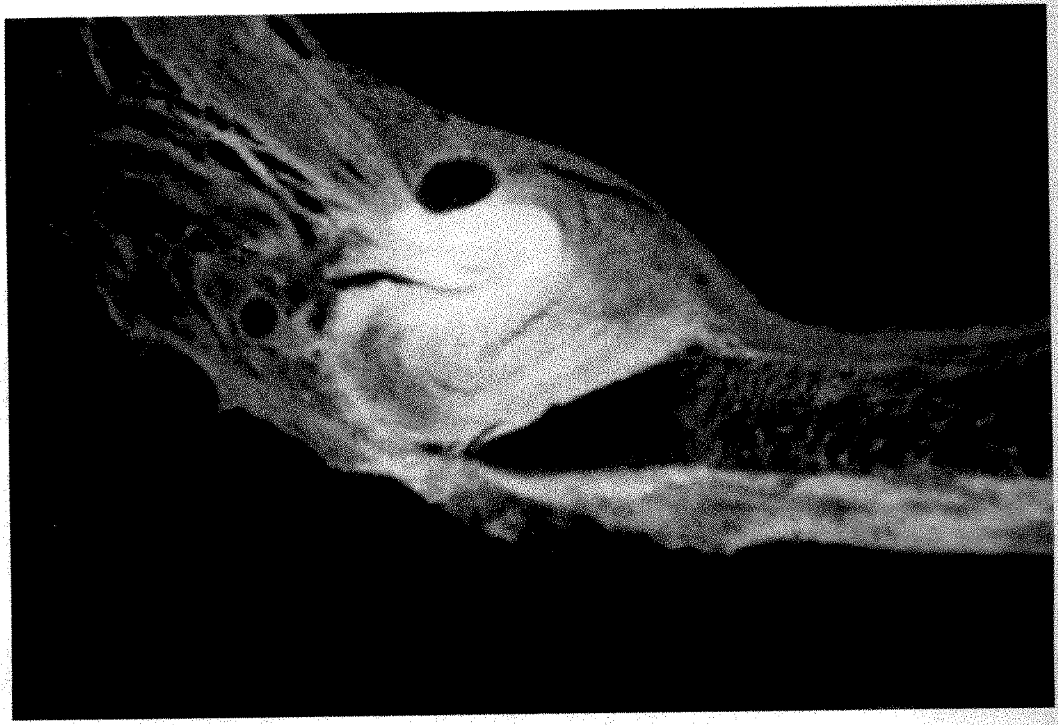


FIG. 3. Photomicrograph, original magnification ×15. Reacted for smooth muscle-derived myosin.[9] Longitudinal section of PTFE–artery anastomosis at zone A at 12 weeks. Lumen is superior. Note the abundant cellular reactivity and luminal protrusion of JNIH.

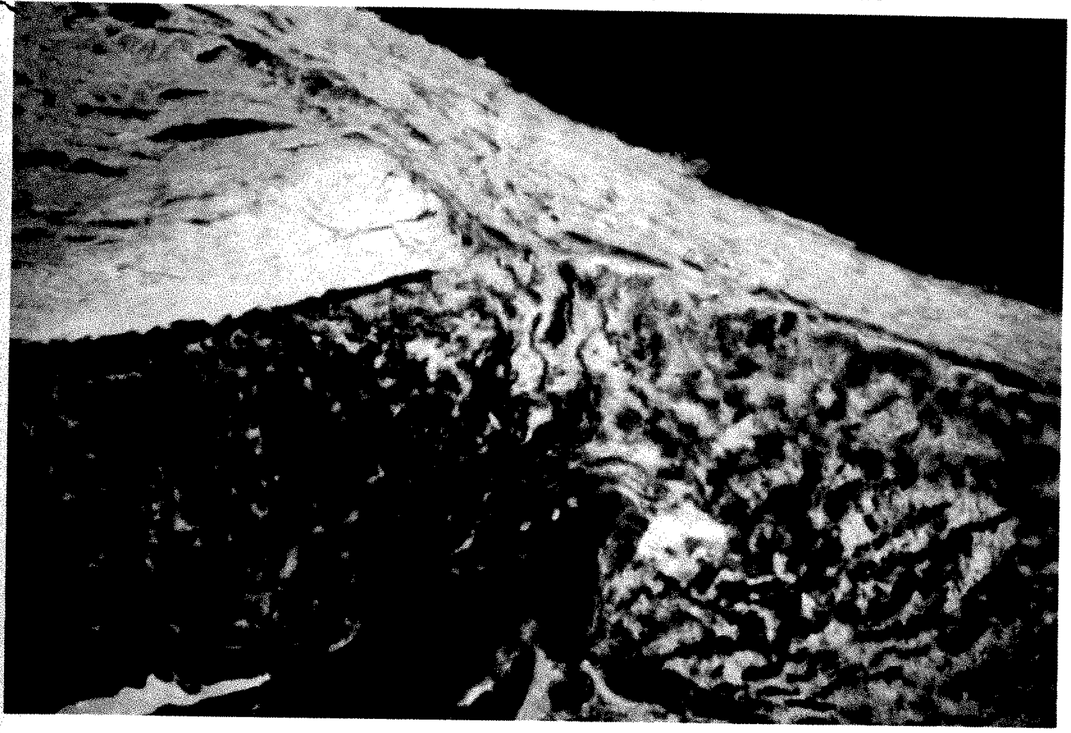
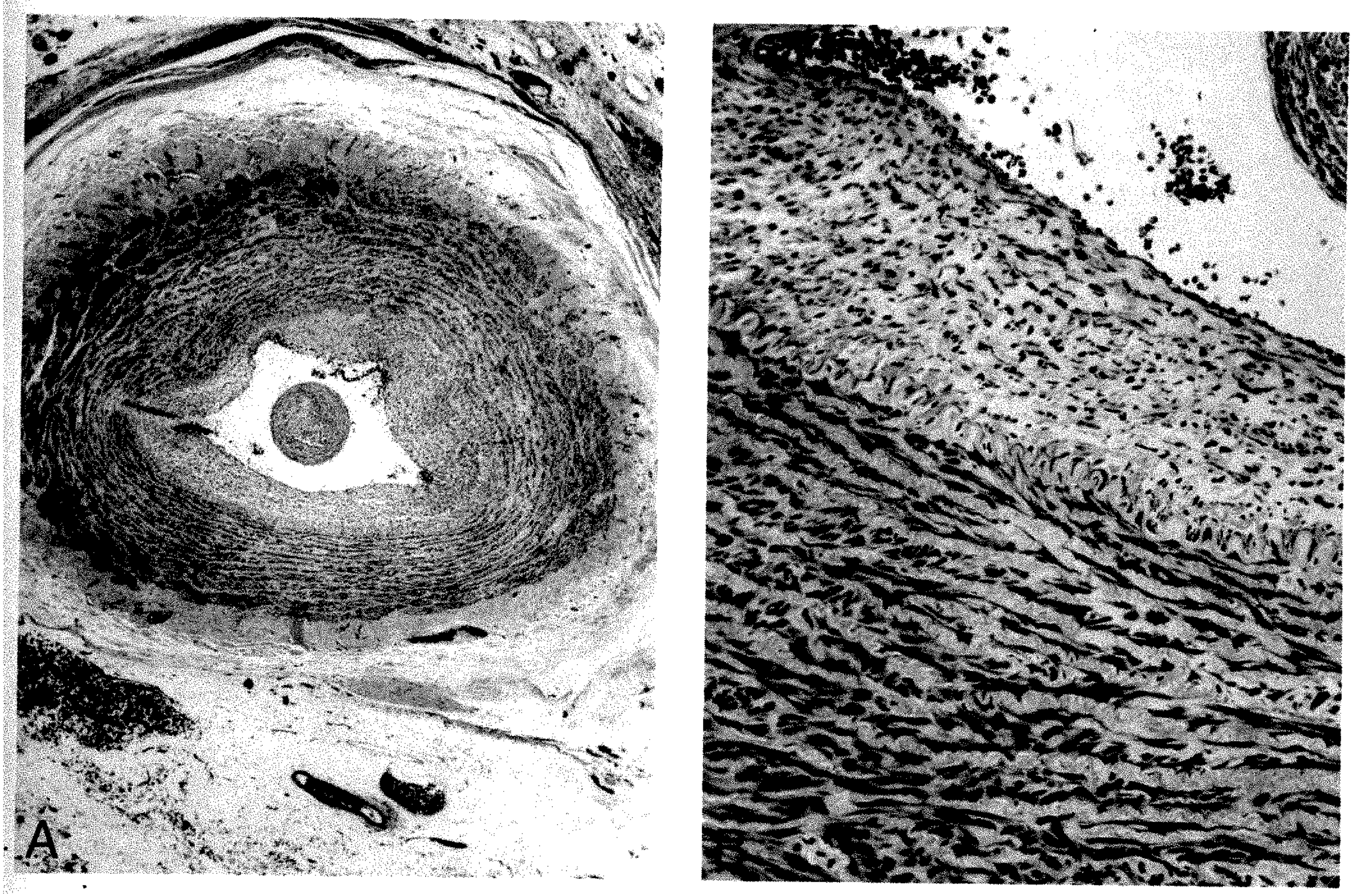


FIG. 4. Photomicrograph, original magnification ×60. Reacted for smooth muscle-derived myosin.[9] Longitudinal section showing PTFE–vein cuff anastomosis at zone A at 12 weeks. Note the scanty cellular proliferative reaction relative to Figure 3.



FIGS. 5A and B. *A*. Photomicrograph, original magnification ×40 H&E. Characteristic A′ diameter of noncuffed anastomosis with stenosis due to juxta-anastomotic neointimal hyperplasia. *B*. Photomicrograph, original magnification ×200 H&E. Enlargement of A′ diameter above. Note the proliferative cellular response in the subintima.

sites and occurs in a variety of arterial locations and grafts, although JNIH related to PTFE in particular has been characterized extensively.[11]

The stenoses in this experimental model appeared mainly to be due to myointimal proliferation. Presumably there is later alteration of smooth muscle cells to cells capable of producing fibrous tissue. The cellular changes promoting the myoproliferative responses are known to begin within several days.[4] The mass of tissue consisted mainly of proliferating smooth muscle or smooth muscle-derived cells, insofar as could be judged in this study rather than by transformation of fibrin clot. However, further studies would be needed to characterize unequivocally all cell types that occur at the junction of the graft and indigenous artery.[12] In the current study the stenotic process was well developed as early as 3 weeks after graft implantation.

Another similarity between the experimental findings in this study and clinical experience was that patency and the development of neointimal hyperplasia were not necessarily concordant. We initially assumed that antiplatelet therapy might retard or neutralize the factor of individual thrombogenicity, as suggested by Freeman and associates.[13] Recent work by Kaplan et al.,[14] however, demonstrated that individual thrombogenic tendencies dominate canine models. It is likely that the aspirin therapy did not eliminate blood clotting factors in the hostile environment of these small caliber grafts. Although 7 of 11 of the cuffed grafts remained patent as opposed to 4 of 11 of the noncuffed grafts, this difference cannot be considered significant due to sample size and known variations in individual thrombogenicity.

Differences in blood coagulability, we believe, account for discrepancies between patency and the development of JNIH both in experimental models and clinically. It is highly probable that increased individual thrombogenicity existed in some of the experimental animals in the current study. This increased thrombogenic potential can give rise to graft thrombosis independently of the development of JNIH. Using the recently described techniques to estimate canine thrombogenicity,[14] we now measure prospectively these factors in this experimental model. Similar measurements might be valuable in humans as well when small diameter prosthetic grafts are required.

Quite separately from the variable of thrombogenicity, vein cuff interposition clearly minimized myointimal proliferation in a quantitatively significant fashion. Figure 6 diagrams a hemodynamic hypothesis based on minimizing graft–artery compliance mismatch as wider dispersion of kinetic energy. It is postulated that the vein cuff more widely distributes kinetic energy from the relatively noncompliant graft to the indigenous artery. The net result is less mechanical arterial wall injury at the end-to-side graft artery junctions, damping cellular responses caused by unfavorable hemodynamics. It is also possible that interposition of venous endothelium in the

TABLE 2. *Time and Patency of Cuffed Versus Noncuffed Grafts*

Time (Weeks)	Noncuff	Cuff
3	Open	Open
4	Open	Open
6	Open	Open
6	Closed	Open
6	Closed	Closed
8	Closed	Closed
8	Closed	Closed
8	Closed	Open
8	Closed	Open
12	Closed	Closed
12	Open	Open

4/11 Open versus 7/11 Open

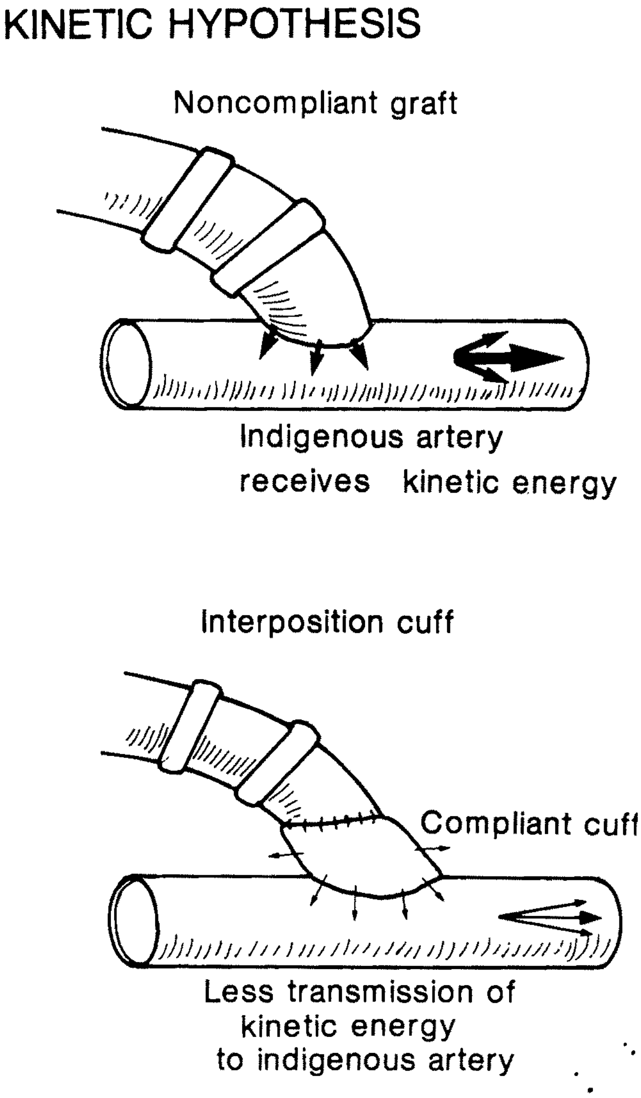


FIG. 6. Diagram of the possible mechanism of action of the vein cuff interposition.

cuff might have mitigated mitagenic factors from the graft, secreted prostacycline or other substances, and exerted still other effects in a purely cellular rather than in a mechanical manner. Currently, experiments are being performed on thrombogenically characterized animals to measure effects of mechanical factors and further define cellular factors that might phenotypically modulate smooth muscle proliferation and secretion.

Acknowledgments

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DISCUSSION

DR. STANLEY O. SNYDER (Norfolk, Virginia): The problem of unsatisfactory long-term patency results with prosthetic grafts at the below-knee popliteal or tibial position has long plagued vascular surgeons. Compliance, the percentage of radial change in response to pressure, is actually an expression of the vessel's elasticity.

Abbott and Bouchier-Hayes[1] demonstrated in canine studies a direct relationship between decreasing graft compliance and decreasing graft patency rates at 2 weeks and 3 months. By decreasing the compliance mismatch between the conduit and the arterial vessel at the distal anastomosis, there was reduction in impedance—that is, a reduction in the opposition to pulsatile flow and subsequent interference with energy propagation.

A 1986 study by Beard et al.[2] demonstrated hemodynamic advantage by adding a compliant vein cuff at the distal anastomosis of vessels 2 mm in diameter. They reported a significant decrease in anastomotic resistance, with an increasingly significant increase in blood flow as blood pressure rose.

Dr. DePalma and his colleagues have conducted a significant research study implicating smooth muscle cells as the culprit in the development of new intimal hyperplasia, previously thought to result from turbulent flow at the site of compliance mismatch of the end-to-side distal anastomotic site.

In 1962, Dr. Andrew Dale[3] reported 16 patients using Teflon to vein composite grafts, but abandoned the technique when only one graft remained patent after 1 year. A similar but slightly modified operative technique first performed in the early 1970's by Drs. Friedman and DeLaurentis, and Rhee,[4] and Drs. Linton and Wirthlin[5] and Dr. Jerry Lord, et al.,[6] produced improved results.

At the 1983 Southern Surgical Association meeting in Hot Springs, Dr. Robert Batson presented a Linton patch technique for overcoming the compliance mismatch, and reported a cumulative patency of 65% after 36 months follow-up.

In 1986, Dr. Buth et al.,[7] of the Netherlands, reported excellent short-term results with tibial bypasses using the umbilical vein graft combined with the short vein cuff; they believed that this technique prevented the thick umbilical vein edges from protruding mechanically in the small arterial lumen.

In Norfolk we have used the beveled end-to-end technique with Goretex™ and as much vein as can be harvested to form a composite graft. Our initial report of 1981[8] revealed a significant increase in patency for 68 composite grafts, compared with 89 all-Goretex grafts.

A follow-up study of 1984[9] again produced satisfactory long-term cumulative patency in 128 composite grafts.

Dr. DePalma's technique will be quite valuable when no adequate vein is available, yet if care is taken to avoid kinking, twisting, or angulation, wouldn't it be preferable to have the Gortex to vein anastomosis and its associated compliance mismatch farther removed from the distal anastomotic site, as it is in the standard composite technique?

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DR. MALCOLM PERRY (Nashville, Tennessee): Neointimal hyperplasia is not a new entity, but the term may be a misnomer, because it is a fibrous proliferation, not an increase in the number of endothelial cells. The widespread use of PTFE has directed our attention to these lesions, since they occur more frequently with these grafts.

The authors have shown that these fibrous lesions appear early, usually in the host artery, opposite the graft. That location and the relative inelasticity of the PTFE have suggested to some people that hemodynamic factors play a central role in the etiology.

This thesis is further strengthened by the observation that inline grafting with an end-to-end anastomosis is rarely compromised, regardless of the material that is used, although fibrosis may be seen from time to time if there are diameter differences.

Through immunofluorescent techniques, Dr. DePalma and Dr. Suggs found that factors from the media appeared to be involved. In the past, we had thought that platelet-derived growth factor was the cause of neointimal hyperplasia. The antiplatelet agents have not lived up to their billing, and have not proved successful in preventing neointimal hyperplasia. This suggests that the more recently described endothelial growth factor may be at fault.

I would like to ask Dr. DePalma if he subscribes to this theory. As one reviews this manuscript, one finds that neointimal hyperplasia was not usually present. Medial hyperplasia is predominant, but some of the slides show intimal proliferation.

Can those mediators that incite cellular growth be blocked? The antiplatelet agents that are available have not been effective in this area.

This is an important study, and although clearly these are preliminary results and lack statistical validity, I would encourage the authors in their line of investigation.

DR. PAUL E. STANTON, JR. (Johnson City, Tennessee): I would like to congratulate the authors on this very well prepared and presented piece of work.

I have another problem area of interest, however, possibly associated with the PTFE graft, that I would like to put as a query to the authors: the PTFE graft's potential association with the acceleration of true atherogenesis downstream from the area of anastomosis.

At one of the national vascular meetings about 3 years ago and as reported in the "Journal of Vascular Surgery" at approximately the same time, Dr. Allan Callow pointed out a series of cases that he had in which, with above-knee femoral-popliteal bypasses, there was what he believed an inordinate number of patients coming back with failure of the graft due to downstream atherosclerotic disease in the midpopliteal segment.

Last year at our institution at East Tennessee State, I had the opportunity to review approximately 150 failed above-knee femoral-popliteal bypasses. It was the philosophy of a previous vascular surgeon at our institution to perform a great number of these above-knee grafts, and interestingly, as we took a large number of early failed grafts (6 months–2 years) back to the operating room and restudied not only the anastomotic area, but the midpopliteal segment, most of these were failing not due to intimal hyperplasia, but due to downstream true atherosclerotic disease.

Presently we have in our laboratory an ongoing series of investigations with an atherogenic animal model in which, over a period of several months, we are evaluating the intimal hyperplastic effects at the anastomotic site, and the downstream effects of accelerated atherogenesis, as well.

To this day, at six months, we have not seen any accelerated atherogenesis downstream. I would like, at this time, to query Dr. DePalma and his associates on whether at the 'A' primed area (or more distally, or perhaps even in the venous cuff segment) they are seeing any early fatty deposition or evidence of fatty streaking that might forebode atherogenic changes.

If they have not noted this, I would recommend that in the future phase of this study this be looked at specifically.

DR. WILLIAM D. SUGGS (Closing discussion): We agree with the points Dr. Snyder has presented. The clinical use of vein cuffs is limited to situations in which there is an inadequate length of vein for a composite graft or for a vein graft failure due to inadequate diameter. In all instances, we would prefer a vein graft for below-knee limb salvage procedures.

In answer to Dr. Perry, with routine histology, we do not see a thick layer of endothelial cells, but note subendothelial collections of cells as smooth muscle or smooth muscle-derived cells.

In answer to Dr. Stanton's question, we have not observed fatty deposits in the A′ diameter, nor have we observed in this model the development of fatty deposits more distally.

We do believe, however, that this experimental model provides a valuable means of studying both neointimal fibroplasia and atherosclerosis in juxta-anastomotic areas.

One Hundred Years of Surgical Management of Hyperthyroidism

ARLIE R. MANSBERGER, JR., M.D.

From the Medical College of Georgia, Augusta, Georgia

"FOR THOUSANDS OF YEARS goiter has been a familiar malady. An unsightly and frequently fatal disease, it was accepted as an inoperable affliction or dispensation of Providence in communities where it prevailed and paraded the streets exciting the curiosity of the populace in towns where it was unusual. The sufferers sought relief from suffocation, difficulty in swallowing, failure of the heart, and from a distressing disfigurement. Thus, this conspicuous tumor of the neck was a perpetual challenge to the physician, and to the surgeon a stigma as well."[1]

Attempts by the ancients to remove diseased thyroid glands were fraught with danger, disaster, and death for patient and surgeon alike. The brief accounts that follow epitomize that dilemma. "In the year 1595, an empiric attempted to remove a goiter in a case of a ten year old girl. She died under the operation, and the surgeon was imprisoned."[1] In quoting a case attempted around 1770, "Such a severe hemorrhage occurred that the surgeon was obliged to stop in the middle of the operation. He was unable to control the hemorrhage by any means. The patient died eight days later."[1] In another case of the same era, "After several fruitless attempts at ligation of the arteries, the severe hemorrhage was controlled by compression day and night during eight days by persons alternating with each other at the task."[1]

When immediate death was not due to hemorrhage, delayed mortality rate of septic etiology was not uncommon. Nathan R. Smith's patient, Mrs. Wells of Prince George's County Maryland on whom the "Emperor" removed a large goiter with ulceration of the dependent skin, died from sepsis on the 13th day after surgery in 1835.[1]

By 1866, the situation was apparently though slightly improved as evidenced by this statement from Samuel D. Gross: "Can the thyroid gland when in the state of enlargement be removed with a reasonable hope of saving the patient? Experience emphatically answers, no! . . . If a surgeon should be so fully foolhardy as to undertake it . . . every step he takes will be environed with difficulty, every stroke of his knife will be followed by a torrent of blood, and lucky will it be for him if his victim live long enough to enable him to finish his hard butchery . . . no honest and sensible surgeon would ever engage in it."[2]

Lister's discovery of antisepsis in 1867 and the development of and use of hemostatic forceps in European clinics (circa 1870) heralded a new era of thyroid surgery. However, in spite of the fact that Theodor Kocher[1] the father of thyroid surgery who in 1872 had became a professor of surgery at the University of Berne at age 31, had accomplished the excision of 101 goiters during the first decade of his tenure with a mortality rate of 12.8% and by 1889 added an additional 250 patients to that series with a mortality rate of only 2.4%; goiter surgery in the United States was a victim of "lag fever."[2]

Souchon[3] in 1896 devoted a few brief comments to the thyroid gland. Souchon stated that the cause of the goiter was unknown but that some believed goiter to be an infectious disease the parasite of which was in the water. He commented that, "the true treatment of goiter consists of extirpation, especially if it grows and if pressure symptoms are serious."[3] It is of interest that Souchon did not mention any specific personal experience with operations upon the thyroid gland in his treatise.

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Charles H. Mayo stated,

> "But a few years ago a reviewer of surgery of this country would have said that the United States was singularly free of diseases of the thyroid gland . . . The surgery of the neck never seemed to enjoy the popularity of that of the abdomen, and goiter operations are not even today sought by the majority of surgeons. Those who were competent did not sufficiently often encourage operative relief until the absolute necessity rendered the mortality so high as to be almost prohibitive. The lay impression became such that operative measures were permitted only in the most advanced cases while semi-surgical, medical, mechanical, and electrical treatment flourished. In most cases, death came slowly and was looked upon as a relief from suffering, a result which satisfied everybody; but the death which follows operation is a shock to all and in but few instances is there a consideration of the fact that medical treatment had previously failed. Neither is the urgent necessity of the operation or the desperate condition of the patient taken into account, but the death has made a debit against the surgical side. Especially is this true in cases of exophthalmic goiter."[4]

In 1906 Mayo reported on the surgical treatment of goiter based upon 300 personal operations[5] and by 1908, he presented a series of 1000 operations upon the thyroid gland.[6] By the time of that presentation, it was clear that the technical problems associated with ordinary goiters, at least in the larger clinics, were no longer barriers to surgical removal. This was true in spite of the large size of many that the patients carried with them to the surgical arena. In Mayo's series[6] of 1000 goiter operations, 574 were cases of simple colloid or diffuse adenomatous goiter with but four deaths, a mortality rate of 0.7%. Crile agreed with Mayo's observations and emphasized that in simple goiters one scarcely accepts a fatality from excision.[7] Both Crile and Mayo agreed that in goiters of the exophthalmic variety, much remained to be done with regard to the reduction of the morbidity and mortality rates associated with operation as a coincidence.

The rigors and awesome responsibilities borne by our predecessors' attempts to reduce the mortality rate of those patients with advanced cases of hyperthyroidism can only be appreciated by a thorough perusal of their efforts as documented in the *Transactions of the Southern Surgical Association.* The problems of therapy were described by Crile who categorized early referrals to his clinic as follows: "Cases with wide-spread degenerations of most of the body, especially of the heart, brain, and liver. They included those emaciated to a skin and bone outline of their former selves; those whose heart spread out flabbily occupying much of the thorax; those with wide-spread edema; those with high fever; those delirious who had to be restrained in bed; those with partial dementia. Certainly, desperate risks; but I argued that if hypersecretion isn't the primary and essential cause of the disease, it was sound reason for thyroidectomy as for other urgent means."[7]

Prior to and even subsequent to the introduction of the preoperative use of Lugol's solution, many innovative means were utilized in attempts to eliminate mortality rate.

Resection of Cervical Sympathetic Ganglia

Removal of the upper and middle cervical ganglia had been advocated by Abadie and Edwards and popularized by Jonnesco and Jaboulay. In 1896 Souchon said, "these symptoms (the symptoms of exophthalmic goiter) are due to changes in the upper and middle ganglions of the sympathetic."[3] He was referring to the theory that exophthalmic goiter was not primarily a disease of the thyroid gland, but a central disease, located in the medulla with its morbid impulses coming through the sympathetic nervous system to produce an excess secretion of the thyroid gland. Mayo argued that cervical sympathetic resection was not as effective as an "operation upon the diseased organ itself."[4] Discussors Carr and Horsley agreed that cervical sympathectomy should be assigned to history and that evidence suggested that the unknown etiology of hyperthyroidism probably resided, as Mayo suggested, in the thyroid gland.

Operative Staging

Operative staging, in which lobar and isthmus resection were preceded by arterial ligation, were described by Kocher and popularized by Mayo. Bartlett,[8] however, must claim the record in the graduated approach to the removal of thyroid tissue in that he had subjected at least one patient to as many as seven operative procedures before the ideal had been accomplished. Those procedures and their temporal sequences were as follows: (1) ligation of the right superior thyroid vessels; (2) ligation of the left superior thyroid vessels five days later; (3) 12 weeks later creation of flaps and muscle dissection and insertion of a pack exposing the right thyroid lobe; (4) 2 days later removal of the right lobe; (5) skin closure 2 days later; (6) 7 months later, left lobe removal; and (7) skin was closure in 48 hours. Further, he stated, "Of course we have frequently ligated both superior thyroids at one sitting and removed both lobes at another hence it will be seen that the graduated approach with us has meant two, three, four, or even more operative stages up to the limit of seven, which is admitted to be the practicable limit."[8]

Roentgen Ray Therapy

Roentgen ray therapy first was mentioned by Mayo in 1905[4] and again in 1906[5] when he described 300 goiter operations, of which 110 were for exophthalmic goiter. In that presentation, Mayo said, "Patients who are not advised to have immediate operation are often kept under observation for weeks until we are satisfied of their ability to withstand surgical treatment. Aside from rest, internal treatment consists of extract of Belladonna, ⅙ grain, with quinine in pill form given three or four times a day. If no improvement is noted, we use x-ray exposure to the extent of skin irritation."[5]

In 1909 Deaver recommended rest and quiet before operation, "It is now evident that x-rays have no specific action in controlling the disease."[9] Richardson in 1922, however, advocated the use of x-ray therapy only for patients with toxic diffuse disease and not for those with "adenomatous goiter with hyperthyroidism".[10] In therapy and its evaluation, he stressed the "availability of adequate, modern, roentgen-ray equipment with the ability to measure dosage" and the use of basal metabolic rate to determine the degree of benefit.[10] Richardson concluded that subtotal thyroidectomy was a more effective form of treatment than x-ray therapy, that roentgen ray had a beneficial effect on certain cases of hyperthyroidism, and that the effect of x-ray was not sufficiently constant to be relied upon as a form of therapy.[10] He mentioned the problem of occasional myxedema and the increased degrees of technical difficulty following the use of x-ray but advocated continued use and study of the modality stating, "In selected cases of exophthalmic goiter, the use of roentgen-ray treatment under careful control was justified for a period of four months during which the patient received about five treatments and finally if after four months of treatment, the degree of improvement in general condition and basal metabolic rate does not promise cure, operation should be undertaken."[10] In discussion, W. H. Wathen believed that, in his experience with over 1000 cases, roentgen ray use was pernicious and had made the technical aspects of the operation much more difficult. He continued to favor preliminary arterial ligation. Mayo agreed and said that although he had in earlier works discussed the use of x-ray therapy in the temporary control of patients with hyperthyroidism, he no longer was an advocate and stated, "If however, they are subjected to three or four months roentgen-ray treatment and then require surgery, I would rather be away from home when they come."[10]

Anoci Association

At the 1912 meeting, George W. Crile urged the exclusion of the patient from psychic stress. Noting that removal of the patient from a stressful environment did not completely eliminate postoperative storm and citing two deaths "from fear of the operation alone,"[11] Crile championed a method of blunting of association impulses by introducing a system of anesthesia designed to minimize the effect of surgical shock. The patient's mind was calmed by the injection of scopolamine and morphine 1 hour before operation. General anesthesia was supplemented by the injection of procaine, which preceded the division of sensitive tissues. Sharp dissection and gentle manipulation were employed, and to minimize postoperative discomfort in serious cases, quinine and urea hydrochloride solution were injected at some distance from the wound. The concept of "stealing" the toxic thyroid was also a Crile innovation.[11]

Injection of Boiling Water

This method of preoperative control was first mentioned as a possibility by Porter before the Southern Surgical Association (SSA) in his discussion of Mayo's paper in 1908.[6] Ten years later, Porter stated, "For the preparation of the substandard risks for major operation, injection of boiling water into the gland substances is more effectual than any other known procedure. In quite a percentage of patients with small goiter of the diffuse hyperplastic variety, injections of boiling water should be the treatment of choice in that it is efficacious and entails less risk and less loss of time than any other method of treatment."[12]

Although Porter utilized the method several hundred times, the first recorded use of boiling water in the *Trans South Surg Assoc* was accomplished by Carr. In discussing Crile's paper concerning psychic stimuli, Carr intimated that he had combined the techniques of anoci association and the use of boiling water. He stated that in a patient with hyperthyroidism and a fibroid uterine tumor, he had operated upon the woman for removal of the fibroid without her knowing that anything was going to be done to the thyroid gland. After removal of the tumor, "I injected the gland with boiling water as suggested by one of our members, while she was under the nitrous oxide anesthesia. She came off the table with a pulse of 80, which had never been under 100 for a year . . . It never went up anymore, and she has been perfectly well ever since."[11]

The introduction of iodine in the preparation of patients for surgical resection of toxic goiter occurred in 1922. McClure in 1926 mentioned for the first time in *Trans South Surg Assoc* the preoperative use of iodine as follows: "The revival of the use of iodine in the treatment of goiter—a treatment as old as the history of medicine—has added much to the success of the operative treatment of Graves' disease as well as in diminishing the amount of colloid goiter."[13]

Sistrunk reported that the preoperative preparation with iodine had dramatically decreased the need for staging.[14] In 1927 1520 patients were operated upon at the Mayo Clinic for exophthalmic goiter and ligations were done in only nine patients; Sistrunk reported further that no ligation had been performed for that disease in the 1928 series.[14] He cited a reduction in the mortality rate to 0.72% and a mortality rate of 0% in those patients operated upon within the first 6 months to 1 year following onset of their disease. He also noted a reduction in morbidity rate, a saving of time and expense with patients because only 8 days to 2 weeks of preparation were required, a diminution of recurrence, and a decrease in the technical difficulties of operation.[14] Sistrunk and Crile agreed in discussion that the use of iodine was the greatest single advance in the treatment of hyperthyroidism and that iodine in many instances was being improperly utilized. The advice given was that if iodine was given for periods longer than 8 days to 2 weeks, the disease seemed to progress to a more active stage, the thyroid became refractory to iodine use with gland enlargement, the metabolic rate and severity of symptoms increased, and the degree of operative risk was accelerated.

The next problem addressed in *Trans South Surg Assoc* relates to the amount of residual thyroid tissue to be left at the time of subtotal resection. The first formal paper on subtotal resection was presented by Bartlett 1916.[15] Bartlett described leaving a residium on each side of the trachea "frequently not larger than a pecan nut, varying, of course, with the original size of the tumor and the character of the material at hand."[15] In the discussion of Bartlett's paper, Finney said that for many years he had been a "heretic in the matter of orthodox ideas and practices and treatment of hyperthyroidism" and had in the preceding 5 years done subtotal thyroidectomies in about 50 patients.[15]

The amount of gland to be resected was stabilized at the Mayo Clinic (circa 1917) and resulted in the then current practice of leaving an amount of thyroid tissue on either side of the trachea that was equivalent to "one-sixth to two-thirds the amount of tissue in a lobe of normal size."[16] That policy, he said had resulted in a significant reduction of recurrences. Furthermore, he stated that the facts (with respect to recurrence rates) did not support extension of the conservative subtotal thyroidectomy and that any such assumption wholly disregarded the fact that recurrences may be secondary to a stimulus or stimuli, that originally caused the disease.

In 1931, Lahey stated that a guide to the amount of residual thyroid remaining following operation related to the degree of involution that did or did not occur in response to preoperative iodine therapy.[17] He referred to a study by Cattel, which showed that involutional response to iodine was evident in 90% and absent in 10% of those treated. Further, he said that iodine involution or noninvolution usually did not occur without clinical evidence of its existence or without gross macroscopic evidence of its presence when a cross section of the gland was made at the operating table.[17] In general, Lahey advised that larger remnants should be left in those who had involuted glands.[17]

In 1930 Lahey called attention to an unusual group of patients who were middle aged or older, who tended to have no exophthalmus, with small thyroid glands, with pulses in the range of 100 to 120 that were neither full nor bounding, with cardiac apex beats that were not forceful, with general motor movements characterized by "definite repose" approaching apathy, and with dry cool skin, an exaggerated appearance of aging, and a lower metabolic rates than that seen in younger patients.[18] Lahey coined the term "apathetic thyroidism" to characterize this panel of patients.[18] He stated that a characteristic of this disease was the fact that it remained undiagnosed for long periods of time and that the unrecognized general deterioration of organ systems was such that these patients had exceedingly high potential for postoperative mortality rates. Thus, he advised that these patients have a two-stage operation for cure, namely, removal of lobes at separate operations 6 weeks apart.[18]

The two-stage operation continued to be utilized also by Lahey in selected thyrocardiac patients.[19] Of 303 patients described, 262 had auricular fibrillation and 41 had normal rhythms but with varying degrees of cardiac failure. Of those with fibrillations, 175 also had "clear congestive heart failure."[19] Lahey advised, "We have repeatedly written on the subject of thyrocardiacs and have presented evidence to prove that patients in seemingly hopeless stages of decompensation can by subtotal thyroidectomy not only have their compensation restored but themselves be rehabilitated to a degree that permits normal activity in most cases."[19] Preoperative preparation was nutritional via diet and glucose, digitalis (for arrhythmia), and Lugol's solution. In a 1933 follow-up study of those 303 patients, fibrillation was restored to sinus rhythm and remained normal in 71.5% and compensation resulted and persisted in at least 95%. The mortality rate was 4.25%.

A natural extension of those good results on thyrocardiacs was a trial of thyroidectomy for patients with congestive failure and with angina who were not afflicted with hyperthyroidism. Thus, Parsons and Parks[20] related their own experiences and those of others gathered via a survey of members of the American, Southern, and Western Surgical Associations who had performed total thyroidectomies for those entities. Data were gathered on 362 patients.[20] Of the 229 patients with cardiac failure, there were 24 operative deaths.[20] The mortality rate in 133 patients with angina was 3.5%.[20] The authors were encouraged by the reported improvement of patients surveyed in spite of wide divergence of opinion by others with respect to the value of the procedure.

Lahey's comments based on personal experience and upon the accumulated reports was less enthusiastic.

> "The number of good results in this series, is in our opinion, not sufficient to make us entirely pleased with them. I do not believe that this operation will endure as a much practiced procedure for the following reasons: First of all, any patients who are operated upon for cardiac decompensation by total thyroidectomy have, of necessity, a very limited cardiac reserve; secondly, one must produce a myxedema, and it is accepted that myxedema is an undesirable state for a decompensated heart. Therefore, it is said that these patients should be given thyroid extract until they are maintained at approximately a minus 25 metabolism . . . this is too complicated a position to maintain with any degree of accuracy, and in the majority of cases . . . they have had a return of decompensation or have died. In the cases of angina pectoris, there have been a few cases who have been distinctively benefited and if a patient is willing to exchange an active state for the sluggish state associated with myxedema, there are undoubtedly certain cases in which the anginal pain can be modified."[20]

In 1938 Laymann and Shearburn,[21] in a well-designed scientific study, were unable to find any quantitative relationship in the duration of preoperative treatment with iodine and the patient's postoperative course, the level of the initial basal metabolic rate, and the patient's postoperative course, or the level of the initial basal metabolic rate and the duration of preoperative iodine treatment.

Cole[22] deprecated the employment of thyroidectomy on patients with neurocirculatory asthenia and pointed out that the differential diagnosis could be made by noting the patient's response or lack of it to iodine therapy. He stressed insulin control of the diabetic patient prior to surgery for hyperthyroidism and noted that insulin requirements in the postoperative period were not infrequently decreased.[22] Cole's was the first mention of negative calcium balance in the hyperthyroid patient, and he advocated the preoperative use of calcium; Cole thought that there were some occasions on which intratracheal anesthesia should be administered, particularly in those with a significant degree of tracheal obstruction, but he was concerned about the surgeon's inability to detect recurrent laryngeal nerve injury during its use.[22]

The issue of staging operations had not suffered its complete demise in 1940, and both Cole[22] and Lahey[23] defended the use of staging in selected patients. By 1940 Lahey had developed a criterion, based on observation of increased oxygen consumption during operation, as a determinant for ending the procedure at the completion of a subtotal lobectomy; he also used a rising pulse rate and increased anesthetic requirement as indications for staging.[23]

In 1946 Lahey reported upon the use of thiouracil, thiobarbital, and propylthiouracil in the treatment of thyrotoxicosis.[24] He had, in the three and one-half years prior to his report, prepared 660 patients with various types of hyperthyroidism and in addition had employed the antithyroid drugs in 21 patients over a lengthy time span to determine whether the medications could be used as a substitute for resection. Lahey stated that all three of the agents were equally effective in reducing the basal metabolic rate, but that of the three agents, propylthiouracil was by far the safest, especially with respect to bone marrow depression.[24] The surgical disadvantages of the thiourea drugs resided in the fact that when patients were prepared solely with one of the drugs, hyperplasia increased, as did the vascularity of the gland, and operating conditions were virtually impossible. Lahey indicated that all the advantages of operating upon a patient freed from toxicity were more than offset by the difficulties encountered (friability of the gland, uncontrollable bleeding and inability to obtain satisfactory anatomic exposure).[24] Omission of propylthiouracil during the final preoperative week and administration of iodine for 3 weeks prior to operation eliminated those disadvantages in Lahey's experience. All eight of Lahey's patients who were pregnant tolerated the drug well, underwent thyroidectomies without indicident, and completed their pregnancies and delivery of healthy babies.[24] Twenty-six patients with diabetes improved, some becoming latent and others requiring less insulin. Of the 21 patients treated for as long as 20 months prior to withdrawal of the drugs, eight had remained in remission and 13 had relapsed at the time of his report. Lahey proposed that permanent cure was not to be expected from the administration of antithyroid drugs alone.

In 1959, Byrd et al.[25] evaluated the results of three modalities of therapy for hyperthyroidism; the use of thiourea derivitives alone, subtotal thyroidectomy following preparation with thiourea derivatives and iodine, and radioactive iodine therapy. There were 100 patients in each group. They concluded that (1) therapy should be individualized and only an occasional patient could be managed with thiourea drugs alone; (2) people with concomitant disease were candidates for therapy with radioactive iodine and/or antithyroid drugs; (3) the use of radioactive iodine was indicated in the rare patient with postresection toxicity; (4) the incidence of hypothyroidism was less after resection than following radioactive iodine therapy; and (5) the evidence justified the continued use of surgery as the basic procedure of choice in the management of the otherwise uncomplicated thyrotoxic patient.[25]

The sole reference to treatment of thyrotoxicosis in children was addressed in 1977 by Hothem et al.[26] in their experiences in managing that disease in 105 patients between the ages of 3 and 18 years.[26] All patients were initially treated with antithyroid drugs. Twenty-six per cent achieved remission on that regimen. Sixty-eight per cent were treated by subtotal thyroidectomy with three patients requiring subsequent therapy with radioiodine. Six per cent were treated with radioiodine with one of those subsequently requiring operative intervention.[26] In the decade prior to their report, there was earlier selection for operation as dictated by their experience. Ninty-one per cent of the males, 89% of children over 11 years of age, and all patients who had no regression of thyromegaly after a sustained period of control received operation or radioiodine therapy. Recognition of the discriminants of age, sex, and failure of regression of thyromegaly, they stated, would permit earlier selection for suitable therapy.[26] Hothem et al.[26] concluded that subtotal thyroidectomy in children had a low morbidity rate and was an effective treatment for thyrotoxicosis in that age group.

The preoperative preparation of patients with thyrotoxicosis took a quantum leap to comtemporary times with the reports by Lee et al.[27,28] relating the use of propranolol. The initial report delivered to the SSA in 1972 related the experience with 20 patients.[27] By 1981 a total of 160 patients prepared with propranolol alone formed the basis of the study and presentation.[28] Lee et al. reported that the beta-adrenergic blocking agent effectively neutralized symptoms of autonomic hyperactivity without significantly affecting thyroid function or levels of thyroxine.[28] The latter observation dictated the postoperative use of propranolol in decreasing doses for 1 week. There were no postoperative cases of storm nor was there any report of morbidity or mortality rates. Thomas and van Heerden in discussion agreed with Lee et al. in general but cautioned that propranolol should not be used in patients with antibodies to beta-adrenergic receptors (*e.g.*, in patients with allergic asthma or with cystic fibrosis).[28] Further, certain patients (a low percentage) did not respond to beta-adrenergic blockade (Thomas). Van Heerden pointed out that there was a synergistic effect when propranolol and iodine were used in combination affecting a greater reduction in T-4 than could be obtained with either alone and said that a combination of Lugol's solution and propranolol was being used at the Mayo Clinic for preoperative preparation. Thomas believed that the fact that patients could be prepared with propranolol alone did not necessarily mean that this was a method of choice for all patients or for all surgeons, and favored a more conventional approach with antithyroid drugs and iodine. Propranolol and iodine were suggested by Thomas for those patients who were intolerant of thioamide drugs.

This record is a brief historical summary of the contributions and courage of those in the lineage of the Southern Surgical Association who, through vision, trial and error, dedication, tenacity, and application of scientific principles, have enabled mankind to conquer a fatal disease, thyrotoxicosis.

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Development of Current Concepts for the Treatment of Breast Diseases as Documented by the Transactions of the Southern Surgical Association

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THE FIRST SCIENTIFIC MEETING of the Southern Surgical Association (SSA) was held in 1888, and all papers presented at this and subsequent meetings were published in the annual bound volumes of *Transactions of the Southern Surgical Association.* In the early years of the SSA, many of the articles published were papers that were read by title and not actually presented or discussed.

Throughout the 19th and early 20th centuries, the prognosis for breast cancer was dismal because of the advanced stage of the disease at the time of initial presentation. Diagnosis was made by clinical examination, and mastectomy was done without prior biopsy confirmation of invasive disease. Breast cancer was not a very popular topic for presentation at the scientific sessions of the SSA, as evidenced by the paucity of papers on the subject during the first quarter century.

It was not until the fourth meeting in 1891 that breast cancer was the subject of a published manuscript. Tiffany[1] identified the differing clinical behavior between lesions that produce skin edema and those that are only attached to the skin. Also, Tiffany accurately defined Cooper's ligaments, although he did not use the term. He pointed out that skin dimpling by scirrhous carcinoma was a consequence of entrapment of these "fibrous" bands within the malignant process.[1]

The first actual presentation on the subject of breast cancer was delivered at the sixth meeting in 1893 by Gaston,[2] who described cachexia that developed with progressive cancer growth. He questioned the rationale of doing an axillary dissection if lymph nodes were involved clinically because chest wall recurrence in such circumstances was 75% in his series. In the discussion that followed, Westmoreland stated an opposing view. He believed that the recurrence rate would be 90% in the axilla if lymph nodes were not removed, and he considered the axillary component of the mastectomy so important that he would do a secondary operation to remove axillary lymph nodes if a patient was sent to him having had only a total mastectomy. Westmoreland also described Rotter's nodes as a potential source of recurrence in a patient who had not had a radical mastectomy.

The report of Gaston contained the results of an interesting questionnaire in the form of a circular letter sent out that same year by Shumway. The operative mortality rate from a radical mastectomy ranged from 10% to 23% (Billroth reporting 23%); the average increase in life expectancy from the operation was estimated at 12 months; and the 3-year cure rates ranged between 9% to 25%. There were no reports of spontaneous cures of breast cancer.

In 1894 Evans[3] reported a single case of simultaneous appearance of breast and uterus cancer. During the same year Halsted[4] and Meyer[5] each published independently and for the first time a description of the procedure of radical mastectomy. Neither Halsted nor Meyer was a member of the SSA.

Because most cancers resected during the 1890s were bulky lesions, wounds were often left open to granulate if skin coverage could not be obtained. Nevertheless, members of the SSA were interested in attempting to improve both the functional and cosmetic result following the treatment of breast cancer. In 1894 Wilson[6] ad-

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vocated coverage of the wound with a split-thickness skin graft, both to impede local recurrence and to improve patient comfort.

Surprisingly, in the 12 meetings of the SSA that were held during the 19th century, only three papers dealing specifically with breast cancer were actually presented, while two more on the subject were read by title. Even more surprising is the fact that in the 10 years that followed, comprising the first decade of the 20th century, not a single paper dealing specifically with breast cancer was presented. It was not until 1910 that the subject of breast cancer was again brought to the attention of the membership. In discussing factors that influence the prognosis of cancer operations, Crile[7] stated that he had cured no patients with breast cancer who had metastasis to the apical axillary lymph nodes. In those individuals in whom the disease was limited to glandular tissue, however, 80% remained alive for a 3-year interval. He considered the most important single factor in the treatment of breast cancer to be early detection prior to the involvement of axillary lymph nodes.[7]

Judd[8] in 1913 reported that breast cancer can recur much later than the customary 3-year interval. Likewise, he argued against the removal of lymph nodes above the clavicle, pointing out that disease in this location represented distant metastasis. His report of 607 patients also dispelled the contemporary theory of the era that breast cancer in young women was uniformly lethal.[8] Table 1 depicts the follow-up study of his patients from 2 to 11 years. Judd described several patients who had a delayed radical mastectomy following biopsy diagnosis and who appeared to have a prognosis equally as good as did those individuals who had an immediate operation.

Chronic cystic mastitis and multiple fibroadenomata presented confusing diagnostic and therapeutic dilemmas to surgeons in the late 19th and early 20th centuries. In 1897 Tiffany[9] described 11 women in their mid-40s who had typical fibrocystic disease and in whom he did total mastectomies. In his opinion, cystic fibroadenoma was either a malignant or premalignant condition, and total mastectomy was necessary to prevent recurrence of the disease.[9] Tiffany thought that a possible etiology of cystic fibroadenoma was the use of suction cups by young women, a practice in vogue at the time, to enlarge the size of the breast.[9]

In 1893 König[10] coined the term "chronic cystic mastitis." He chose the term because he considered this pathologic process to occur secondary to a "vicious cycle of secretion and irritation."[10] In 1910 MacCarty[11] first used the term "chronic cystic mastitis" but noted that some cells did penetrate the basement membrane. He considered these cells to represent invasive breast cancer at its earliest stage and recommended radical mastectomy as the treatment of choice.[11] MacCarty expanded his report before the SSA in 1913.[12] He identified primary, secondary, and tertiary ductal hyperplasia and recommended simple excision for primary hyperplasia and radical mastectomy for the tertiary variant. For women under 35 years of age, he recommended a total mastectomy for secondary hyperplasia for both diagnosis and treatment. For older women, he recommended a partial mastectomy for diagnosis and, when tertiary hyperplasia was identified in the specimen, a radical mastectomy was considered appropriate therapy.

TABLE 1. *End Results: 514 Determinant Cases*[8]

	% Survival (2–11 years)
Dead of other causes	4.1
Alive with breast cancer	7.3
Dead of breast cancer	47.6
Alive and well	41.0

Thus, as early as 1910, pathologists had identified *in situ* breast cancer and had predicted a spectrum of morphologic changes in ductal cells that ranged from atypical hyperplasia to invasive breast cancer. During this era, both surgeons and pathologists realized that early diagnosis was essential to ensure survival for patients with breast cancer. Nevertheless, MacCarty, for the first time at the SSA, questioned the advisability of completing a total mastectomy for apparent benign conditions such as primary hyperplasia.

In 1920 Bloodgood[13] catalogued the differential diagnoses of 350 benign operative specimens (Table 2). Bloodgood appropriately indicated that chronic cystic mastitis was not a precancerous lesion and, therefore, did not require mastectomy. The entire breast was available for examination in 222 of the 350 specimens. Obviously total mastectomies had been done. There was no gross or microscopic evidence of cancer in any of these specimens. Bloodgood did, however, continue to make the diagnosis of cancer on clinical grounds alone and was willing to recommend a mastectomy solely by this mechanism. His clinical diagnostic criteria for identifi-

TABLE 2. *Pathology of Chronic Cystic Mastitis*[13]

Blue dome cysts	174
Galactocele	8
Multiple blue dome cysts	28
Nonencapsulated adenomatous areas	48
Nonencapsulated chronic cystic mastitis containing minute cysts or dilated ducts	39
Diffuse dilation of ducts	22
Nonencapsulated cystic adenomas	18
Senile parenchymatous hypertrophy	13
Total	350

cation of benign disease were as follows: (1) a patient less than 25 years old; (2) tumor present 2 years or longer without growth; (3) multiple tumors—particularly in both breasts; (4) single definite nodule associated with indefinite nodules; and (5) no definite tumor but multiple indefinite nodules. Further, he would recommend radical mastectomy if microscopic examination of the tissues in any of these clinical presentations was doubtful.

In 1921 the treatment philosophies espoused by Bloodgood were echoed by others. Peck of New York in discussion of Bloodgood's second presentation[14] before the SSA emphasized that "there is no excuse for doing a radical operation for benign lesions if reasonable care is taken in making a diagnosis, local removal of the mass being quite sufficient." Also, in discussion of Bloodgood's presentation, Finney commented on the success of educational programs to alert women to the early diagnosis of breast cancer. He found that the diagnosis of breast cancer was becoming more difficult because women were reporting to his office with "imaginary tumors." Early in his career, he pointed out, diagnosis of breast cancer was easy to make clinically because women reported initially with advanced stages of disease. Such a situation in 1920 was no longer the case.

In 1928 Deaver[15] challenged the precancerous nature of any benign condition and strongly stated that mastectomy should not be done, especially in young women, until cancer was proven by microscopic section. He recommended that biopsy be done with a small rim of normal tissue, and that the surgeon change gloves before closing the wound to prevent implantation of healthy tissues with cancer cells. Deaver reported an 8-year follow-up study of 242 patients operated upon with benign conditions in whom no malignancy had developed.[15]

By the mid-1920s, radiation therapy either before or after operation was becoming popularized and advocated in European and American clinics. In 1926 Ochsner[16] condemned x-ray therapy; he considered it to be of little value and potentially harmful because of the morbidity of local complications. Deaver[15] postulated in 1928 that radiation therapy may cause lymphedema of the arm, but he also had seen treatment with radiation therapy cure arm lymphedema when it was secondary to recurrent cancer in the axilla. In 1928 Crile[17] supported the use of postoperative radiation therapy. His disease-free survival for 4 years with and without radiation therapy was 25.9% and 24% respectively. These data did not convince the SSA membership, and in 1931, in a discussion of a presentation by McClure,[18] Trout, a previous advocate of radiation therapy, indicated that he could find no objective evidence that survival had been increased by the use of this adjuvant therapy. Likewise, he was surprised to find that throughout the United States some radiotherapy machines were improperly calibrated and were causing chest wall burns.

Lee made several important contributions to the understanding of the biology of breast cancer. In presentations before the SSA in both 1929[19] and 1932,[20] he pointed out the influence of axillary metastasis on prognosis. The overall 5-year survival rate of his patients was 41%. Patients with positive axillary lymph nodes had a 5-year survival of 23% *versus* 72% in those with negative nodes. The quadrant of the breast in which the breast cancer arose had no influence on survival. He noted that in the immediate past, surgeons had been operating upon virtually all stages of breast cancer and believed that the more advanced forms should be treated by a combination of palliative surgery and local irradiation. He defined inoperability as fixation to the chest wall, multiple cutaneous nodules, extensive axillary metastases with a swollen arm, positive supraclavicular lymph nodes, and distant metastases. McClure[18] and Nicolson[21] presented data substantiating the results reported by Lee. In multiple presentations by different authors before the SSA for many years to follow, Lee's criteria of inoperability were applied to define their populations.

The etiology of breast cancer had been discussed by several authors. In 1913 Bryan[22] expressed the idea that trauma was responsible for 13% of female mammary cancer and for 50% of male cancer. In 1933 Trout[23] was a proponent of the lymph stasis theory because many women with carcinoma of the breast had a history of some dysfunction affecting the breast, such as irregularity of lactation, abscesses, definite trauma, infected nipple, *etc.* He pointed out that the incidence of carcinoma of the breast in Chinese women was much higher than any other race and likewise noted that a flat chest in this race was regarded as a very prized possession. Trout suggested that binders on the breasts of Chinese women might produce trauma and stagnation. In 1933 Bullock[24] thought that closely fitted clothing might increase lymphatic stagnation in the breast, and Adair[24] described a laboratory experiment in which ligation of the terminal ducts of the nipple in mice increased the incidence of spontaneous mammary cancer from 5% to 87%. He was convinced that the advice given to mothers by obstetricians to avoid nursing and subsequent lactation was incorrect, as resultant stagnation of milk within the ducts was a major contributor to the etiology of mammary cancer. In 1935 Nicolson and Berman reported that the lactating breast was less likely to develop carcinoma than a nulliparous breast.[25] The largest per cent of breast cancers in their series occurred in the upper outer quadrants, possibly explained, in their opinion, by the imperfect lymphatic drainage in this portion of the gland due, in turn, to poor support of the breast. The authors felt that the proper type of brassiere, supporting but not constricting, would reduce breast lesions and would consequently lower the incidence of malignancy. In 1937 Cohn[26] retrospectively compared the indigent white and black populations at Charity Hospital to identify any epidemiologic or possible etiologic differences. Long-term survival data were not available, but there was no difference in the clinical behavior or natural history of the disease based on race alone.[26]

In 1934 Rodman[27] defined the morphologic changes that occur in chronic cystic mastitis. He correlated these changes with the menstrual cycle, thereby identifying the alteration in hormonal milieu as etiologic in this benign disease. He recommended local excision for adenofibromas. For patients with chronic cystic mastitis under the age of 35, a breast mass was observed through two menstrual cycles, and if it did not change appreciably, it was then removed by excisional biopsy for microscopic study. For women over 35 years of age, and in whom the mass did not change appreciably, amputation of the breast with pathologic examination of the whole specimen was recommended as it had been in the past. If breast cancer was identified, then a radical operation was completed.

In 1943 Cole and Rossiter[28] classified chronic cystic mastitis into four types (Table 3). They pointed out that two or more of the four types were often encountered in a single biopsy specimen. Precancerous hyperplasia was often seen in close proximity to frank, invasive breast cancer, and cancer often developed in breasts known to harbor precancerous hyperplasia identified by a previous biopsy. Cole and Rossiter doubted the validity of frozen section diagnosis for precancerous hyperplasia and, although the resemblance to cancer at times was remarkable, they did not think that a diagnosis of cancer was justified without the pathologic criterion of invasion.[28] Cole summed up their thoughts as follows: "If you cannot be sure about the diagnosis, and fear cancer, the breast should be removed or a very wide excision done."[28] They urged, however, to improve diagnostic ability so that every nodule of the breast did not need removal.

TABLE 3. *Chronic Cystic Mastitis: Classification*[28]

1. Adenofibrosis
2. Benign parenchymatous hyperplasia; no atypical change
3. Precancerous hyperplasia; advanced proliferation of cells with layering and increased mitoses; no invasion
4. Cystic disease; no epithelial hyperplasia

In 1939 Brooks and Daniel[29] presented the status of radical mastectomy at Vanderbilt. The Halsted radical mastectomy was beginning to be questioned by other authors. In Britain, some surgeons were performing a simple mastectomy or lumpectomy alone. Only 33% of patients with positive lymph nodes in the Vanderbilt series survived. Nevertheless, the authors concluded that "these patients could not have been cured of the disease by simple mastectomy and all of [our] experience has been contrary to the view that as good survival periods could have been obtained by the employment only of conservative operations."[29] Marshall and Hare[30] condemned the use of the simple mastectomy alone as treatment for carcinoma of the breast, noting that patients with extensive axillary involvement could be salvaged by radical mastectomy, particularly when combined with appropriate roentgen ray therapy. Trout[31] likewise reported both his and his father's patient series from 1909 until 1950. He noted that from 1909 to 1920 there were 152 patients in whom the 5-year survival rate was 22%. From 1924 to 1928 there were 86 patients, and during this time roentgen ray therapy was added. The 5-year survival rate increased to 55%. In the most recent series of 195 patients, 5-year survival rate was 81% for patients with negative axillary lymph nodes and 40% for patients with positive lymph nodes. Thus, enthusiasm for adjuvant radiation therapy was rekindled.

In the early 1950s modern concepts emerged for the management of benign and malignant breast diseases. Between 1946 and 1952, Harrington[31-33] presented the long-term follow-up data for over 6000 patients treated by radical mastectomy at the Mayo Clinic (Table 4). These reports emphasized that breast cancer will recur throughout the lifetime of the patient and gave credibility to the concept that the most common cause of death in a patient with breast cancer between 5 and 10 years following diagnosis is, in fact, from metastatic breast cancer. This large study reconfirmed that the most important prognostic indicator was the presence or absence of axillary nodal metastasis. The degree of anaplasia and age at diagnosis were also considered important. For example, elderly patients with high-grade lesions had a better prognosis when compared to younger patients with an equal degree of anaplasia in the primary malignancy. In 1952 Goode and Martin[34] made several important observations. The first symptom in 44% of their patients was pain. The authors pointed out the obvious error of considering benign lesions painful and malig-

TABLE 4. *Follow-up Study of 6149 Patients Treated by Radical Mastectomy*[32]

Survival (years)	− Nodes (%)	+ Nodes (%)
5	75.5	30.4
10	57.9	16.4
15	44.4	11.1

TABLE 5. *Surgical Experiences with Mammary Cancer*[34]

Stage	Definition	Five-year Survival (%)
I	Limited to breast	82.4
II	Small axillary nodes	43.8
III	Multiple axillary nodes	29.4
IV	Distant metastasis	1 of 5 patients

nant lesions insensitive as an all-or-none phenomenon. Likewise, when the surgeon and pathologist were in doubt about the frozen section diagnosis, these investigators considered it far wiser to close the wound and wait for permanent sections than to proceed with a simple mastectomy. Goode and Martin noted no appreciable effect on the 5-year survival with a delay of 48 hours to await permanent section in inconclusive situations.[34] Postoperative roentgen ray therapy did not appreciably enhance the 5-year survival rate for those patients who had positive axillary nodes. For the first time, a staging system was presented to the members of the SSA, reflecting those used currently (Table 5). The philosophical concept that breast cancer was a systemic disease and potentially unaffected by local treatment had arisen. Patients with untreated breast cancer had a 5-year survival rate of 22%, whereas the authors' overall 5-year survival rate was 64.4%. These data suggested that the surgeon does play a major role in the treatment of primary breast cancer and that delay in therapeutic intervention increased patient morbidity and mortality rates.

In 1952 Copeland,[35] in discussing Kerr's presentation, described the role of progesterone and estrogen in the stimulation of hypertrophy and hyperplasia of both duct and lobular cells. He concluded that an imbalance of these two hormones was reflected as chronic cystic mastitis. His recommendation, and that of Kerr,[35] was to aspirate large cysts, and if the fluid was clear and the cyst disappeared, no further therapy was necessary. Only 0.89% of cysts had an associated cancer.

In 1956 Alrich et al.[36] reported the results of radical mastectomy at the University of Virginia. The number of positive axillary lymph nodes and 5-year survival rate was the same regardless of the breast quadrant in which the cancer developed. The authors noted that simple mastectomy offered little more than palliation except in patients with early adenocarcinomas. In 1956 Byrd and Stephenson[37] reported on the experience with simple mastectomy for carcinoma of the breast at Vanderbilt. The original intent of the review was to identify the indications for simple mastectomy because the operation was used at Vanderbilt primarily for palliation. The authors found, however, that 23.7% of their patients had lived for 5 years or longer. Nineteen of 27 patients (70.4%) who had no metastasis at the time of operation lived for more than 5 years and only one developed a recurrence. Of the 102 patients with clinical metastases at the time of operation, 15.7% lived longer than 5 years. This report established that in certain circumstances simple mastectomy could achieve long-term survival in select patient subsets.

TABLE 6. *Comparison of Survival: Simple* vs. *Radical Operation*[38]

Three years	Radical (40)	Simple (56)
Overall survival	75%	80%
Disease-free survival	63%	71%
Four and one-half years	**Radical (27)**	**Simple (29)**
Overall survival	59%	69%
Disease-free survival	52%	66%

In 1960 Crile[38] reviewed the mounting world literature indicating that limited procedures followed by radiation therapy would result in similar 5-year survival rates for small breast cancers as would radical and ultraradical mastectomies. He emphasized that the medical profession should pay less attention to the possible involvement of lymph nodes by tumor and be more cognizant of the potential immunologic role that lymphocytes in these nodes play in the body's defense against cancer cells. In data from radical mastectomy specimens, Crile noted that 32% of patients with clinically negative axillae had histologically positive nodes, whereas only 22% of clinical Stage I patients, when treated by simple mastectomy and without radiation therapy, later developed clinically positive axillary nodes.[38] These patients were treated by a delayed axillary dissection. At the 3-year interval, disease-free survival was the same in both groups despite an average delay of 14 months between mastectomy and axillary dissection (Table 6).

A heated discussion was generated by Crile's paper.[38] Dumphy suggested that these patients were highly selected and praised Crile for his astute clinical judgement. He warned, however, that the data should not be accepted until a double-blind, randomized study was completed to evaluate the hypothesis. Criticisms by Firor were read by Blalock. Firor was critical of the small number of patients in each category, the short time of observation, and the heterogeneity of the two groups being compared. His most serious criticism was, however, "the immense harm that could result from an internationally famous surgeon's seeming to advocate an inadequate operation for the eradication of carcinoma of the breast."[38]

In 1959 Copeland and Higgins[39] addressed the diagnostic problem of nipple discharge. In patients between the ages of 20 and 49 years, discharge from benign lesions exceeded that from malignant ones by a ratio of 2:1. In the age group between 50 and 79 years, discharge from the nipple assumed an increasingly serious significance with the ratio being reversed in favor of malignant lesions. Bloody nipple discharge did not occur as a consequence of breast cancer in patients under the age of 30, and in those between 30 and 49 years of age, a bleeding nipple was most often associated with a benign condition. Bloody discharge in patients over 50 years of age, however, was associated with malignant disease in eight of 11 patients. McLaughlin et al.[40] noted a similar relationship between age and etiology of nipple discharge, and recommended a particularly aggressive approach to bloody nipple discharge in patients without a palpable mass who were over the age of 50 years. Simple mastectomy was considered justified to permit thorough examination of the breast. In the discussion, Bowen described a patient in whom the offending duct had been identified by cannulation with a probe immediately prior to exploring the subareolar area.

Sparkman[41] in 1961 explored the recent suggestion that false-positive frozen section diagnoses were leading to unnecessary radical mastectomies. Combining his experience, in which there were no false-positive diagnoses, with that of his colleagues in Dallas, the known incidence of unnecessary radical mastectomies per surgeon occurred once in every 167 years of practice. He concluded that frozen section remained a reliable diagnostic tool if the surgeon and pathologist were willing to defer an inconclusive result.[41]

For the remainder of the 1960s, several interesting papers were presented. Byrd et al.[42] updated the experience of the Vanderbilt Hospitals with a report of 1765 cases of breast cancer. Age had no effect on prognosis regardless of nodal status; the incidence of bilateral breast cancer was 2.5%. Horsley et al.[43] identified 67 patients, (4.3% of the Virginia series) with breast cancer who were 35 years of age or younger. The absolute 5- and 10-year survival rates were the same as the entire age spectrum of patients with this disease. All 12 pregnant patients survived 5 years. Byrd et al.[44] in 1961 reached the conclusion that pregnancy and lactation did not necessarily impart a poor prognosis for breast cancer. There was no maternal mortality, and one fetal death occurred in the 29 reported patients. Patients with positive axillary nodes had a 5-year survival of 28%, whereas all 11 patients with negative lymph nodes survived a minimum of 5 years.

In 1968 McLaughlin and Coe[45] updated their consecutive series and noted that the presence of one to three positive lymph nodes in the axillary specimen did not statistically alter survival when compared to patients with negative axillary nodes. Bilaterality of breast cancer was becoming of interest. In their series, 4.5% of the women developed bilateral breast cancer from 1 to 20 years after initial treatment.[45] In 1969 Finney et al.[46] reported an 8% incidence of bilateral breast cancer in a personal series. They also compared simple *versus* radical mastectomy. The cumulative probability of death from cancer in the two groups was similar for the first 10 years after operation, but after this time, the death rate in simple mastectomy patients increased remarkably above that for individuals having radical mastectomy. The authors concluded that patients with long life expectancy should be treated by radical mastectomy and that these results cast some doubt on the theory that lymph nodes within an intact axilla act as a defense against the spread of cancer.[46] Likewise, the authors pointed out that patients with four or more positive lymph nodes had a worse prognosis than those individuals with negative nodes or one to three positive nodes; yet, those patients alive after 5 years had the same probability of long-term survival regardless of lymph node status.[46]

In 1969 Amerson[47] reported seven adolescent females who had large lesions characterized by increased stromal cellularity and epithelial hyperplasia. The diagnoses were benign cystosarcoma phyllodes or giant fibroadenoma. This paper was important because it pointed out that adolescent females often have giant lesions in the breast that are benign, and that local excision maintains breast architecture without a recurrence. Nance et al.[48] reported 53 patients with Paget's disease of the breast. Sixty-one per cent of the patients had an underlying mass, and 40% had symptoms lasting longer than 1 year, usually secondary to a failure in diagnosis by the initial physician. All patients had at least a total mastectomy, and cancer was found in all but one specimen. Ninety-four per cent of the invasive carcinomas were within a palpable mass, and pagetoid change in the nipple was not a detrimental prognostic variable.

Madden et al.[49] presented their classic paper before the SSA in 1971. Ninety-three patients were reported who had neither pectoralis major nor minor muscles removed. Madden et al.[49] did not think removal of apical axillary nodes was valuable necessarily and identified no positive Rotter's lymph nodes in any of these dissected specimens. Also, lymphangiograms done before and after operation indicated that this operation removed all axillary contents. Five- and 10-year survival and local recurrence rates for the patients were similar to those for patients undergoing extended radical mastectomy. In 1978 Baker et al.[50] reported a comparison between modified radical mastectomy and radical mastectomy that revealed no statistically significant difference in 5-year survival for patients with Stages I, II, or III breast cancer. There was a significantly greater incidence of local recurrence in the axilla and mastectomy scar for Stage III patients treated by modified radical mastectomy. The authors postulated that the axillary nodal recurrences were secondary to inadequate dissection of the axilla, and recommended removal of the pectoralis minor muscle, apical axillary contents, and Rotter's nodes in patients with Stage III disease. In the discussion, Sanders emphasized that physicians who choose modified radical mastectomy make the decision subconsciously that the pectoralis major muscle and fascia are not involved. In a consecutive series of 105 patients who underwent radical mastectomy, he identified a 19% incidence of unsuspected involvement of the pectoralis major muscle and/or fascia by breast cancer.

After reports of the results from modified radical mastectomy[49,50] no further consecutive series of patients with operable lesions were reported before the SSA in an attempt to define the proper operation. The membership turned their attention to diagnostic tests, estrogen receptors, hormone manipulation, breast reconstruction, and the contralateral breast.

Preoperative Radiation Therapy

In 1939 Trout[51] reviewed the indications for preoperative radiation therapy. He included patients with large axillary nodes, lesions fixed to the skin, locally advanced disease that precluded surgical removal, and potential for carcinoma to be within a biopsy wound. For the first time before the SSA, an author concluded that proper radiation therapy to the chest wall aided radical surgery only in the prevention of local recurrence, and not in cures. In 1961 White et al.[52] reported a reduction in local recurrence rate following preoperative radiation therapy for locally advanced breast cancers. They proposed that residual disease after mastectomy was the most common cause for recurrence on the chest wall. The recurrence rate using their technique was only 5.2% compared to a 19.2% recurrence rate in individuals with similar lesions who did not receive preoperative radiation therapy. Townsend et al.[53] in 1984 reported 53 patients with locally advanced breast cancer who, likewise, had 4500–5000 rads of radiation therapy after operation. Eleven per cent of their patients developed chest wall recurrence. In discussion, Copeland presented two groups of patients; each had grave signs, but one group was technically suited for a total mastectomy and Level I lymph node dissection, whereas the second group was technically unsuitable but, nevertheless, had the same operation. Both groups received radiation therapy after operation. With a minimum 10-year follow-up evaluation, chest wall recurrences were 6% and 14% respectively, and the 10-year survival rates were 39% and 23% respectively, with no adjuvant chemotherapy. Copeland presented these data to indicate that control of chest wall disease in locally advanced breast cancer does result in, at least, some long-term survivors without the use of systemic chemotherapy. The most efficacious method of treating locally advanced breast cancer was with multiagent chemotherapy initially, followed by total mastectomy with Level I lymph node dissection, and then postoperative radiation therapy to the chest wall and supraclavicular, axillary and internal mammary lymph nodes.[53]

Hormonal Therapy

The treatment of carcinoma of the breast with estrogen was reported initially by Marshall and Hare.[30] They proposed that estrogenic compounds blocked the pituitary secretion of follicular stimulating hormone, thereby allowing tumor regression. In the same year, Horsley[32] reported a series of patients in whom he combined bilateral oophorectomy with radical mastectomy. Although the number of patients investigated was too small to be conclusive, he considered the survival results outstanding. In discussion, Lehman chastised Horsley for not presenting comparisons of cure rates in premenopausal patients with and without castration and for not correlating survival with extent of disease at the time of surgical treatment because it may have been more influential than castration on 5-year survival in this small series of patients.

In 1961 Horsley and Horsley[54] reported a series of 72 premenopausal patients who were treated by radical mastectomy and bilateral oophorectomy and followed for a 20-year period. Survival rates for patients with no axillary metastases were 91% at 5 years and 61% at 10 years. Those individuals with positive axillary nodes had a 5- and ten-year survival of 50% and 30%, respectively. Survival rates were comparable to women in the postmenopausal age group. Alrich and Hairston[55] reported a nonrandomized comparison of patients with and without oophorectomy treated at the University of Virginia (Table 7). When patients were stratified according to risk, prophylactic oophorectomy improved the overall survival by 10% and prolonged the disease-free interval in patients who subsequently relapsed.

In 1970 Horsley et al.[56] reported on 111 patients with skeletal and soft-tissue metastases treated by adrenalectomy. For those patients with a disease-free interval greater than 2 years, 68% responded, whereas those with an interval less than 2 years had only a 32% response rate. Fifty per cent of the responding patients were alive 2 years after adrenalectomy, whereas, only 24% of nonresponders survived 2 years. Adrenalectomy usually followed a prophylactic oophorectomy done at initial treatment of the primary disease. The authors concluded by recommending bilateral oophorectomy in the premenopausal patient with metastatic disease, and, if an objective response was obtained, then adrenalectomy was indicated after relapse. In the postmenopausal patient, adrenalectomy and oophorectomy were recommended at the time metastatic disease to bone or soft tissue was diagnosed. Horsley et al.[56] also found that the addition of 5-fluorouracil to their therapeutic regimen was beneficial. Multiple investigators confirmed these observations; in 1977 Wells et al.[57] reported the ability to medically suppress adrenal function with aminoglutethimide. Steroid suppression was reversible once aminoglutethimide was withdrawn. A previous response to hormonal therapy correlated with a higher incidence of complete or partial remission, an indication that estrogen receptor, a new technique at the time, might be predictive of response rates. In the discussion, Horsley said that he was using aminoglutethimide as a test mechanism to see which patients might respond to surgical adrenalectomy.

In 1952 Kerr[35] first reported the use of estrogen for the diagnosis of benign breast diseases. Oral estrogen frequently eliminated breast pain and was associated with softening or disappearance of breast masses. In only two of 575 patients, dissolution of various cystic disease masses left a single mass, which on biopsy proved to be malignant. A 2- to 20-year follow-up study did not reveal a single case of malignant disease following disappearance of a mass in response to estrogen therapy.

Byrd et al.[58] analyzed 713 patients who took an average daily dose of 1.25 mg of equine estrogen for 9 years or more. There was no increase in mammary cancer in this patient population and there was no increase in the death rate from breast cancer when it did occur. The patients, in general, enjoyed a much lower mortality rate overall than would be expected from the available population data, primarily from a decrease in mortality rates from all cancers, heart disease, and stroke. Byrd et al.[59] updated this review in 1976 with a report of 1116 patients followed between 5 and 28 years. New information suggested that women who had been receiving estrogen therapy and were nulliparous had a higher than predicted risk of developing breast cancer during the first 10 years of estrogen ingestion. Following this 10-year interval, however, the risk became similar to that of other patients from this study population. Gray and Hoover[60] in 1977 reported a follow-up study of 1891 patients who took oral conjugated estrogens. The overall risk for breast cancer was 1.3 times the general population, and it appeared that higher dosages of hormone therapy might result in an increased risk. There was a protective effect from multiparity and oophorectomy that disappeared after 10 years of therapy. A risk increase from nulliparity was not demonstrated in this study. The risk:benefit ratio favored the ingestion of estrogenic compounds in postmenopausal women without a substantial escalation in risk for the development of breast cancer.

TABLE 7. *Prophylactic Oophorectomy: Five-year Survival Rates*[35]

Without oophorectomy	
− Nodes	70
+ Nodes	47
With oophorectomy	
− Nodes	81
+ Nodes	65

Values are given as percentages.

Diagnosis

In 1972 McClow and Williams[61] compiled mammographic data from 3030 consecutive patients. Of 191 breast cancers identified in these patients, 35 (21%) were not palpable clinically, and 156 had symptoms and/or physical findings that would have initiated a biopsy in the absence of mammography. In this latter group, 11% of the cancers would have been missed by mammography alone. The authors concluded that for maximum diagnostic accuracy, both physical examination and mammographic criteria for biopsy are necessary.[61] In 1973 Shepard et al.[62] reported the diagnostic accuracy of mammography to be 80%. The rates of false-positive and false-negative diagnoses were 14% and 6%, respectively. Shepard distinguished between benign, large, dystrophic calcifications and fine stippled microcalcifications in localized areas that were characteristic of malignancy.

In 1985 Letton[63] reported a 100% follow-up study of 8058 women screened by mammography with a 10-year median duration of follow-up. Of the 912 women biopsied, 122 were found to have breast cancer. Thirteen had died by the time of the report. Eight cancers (6.6%) were found by clinical examination that were not detectable by mammogram. In 1986 Symmonds and Roberts[64] addressed the problem of diagnosis of nonpalpable breast abnormalities identified by mammogram. Needle localization was used for 499 breast biopsies. Seventy-two (14%) cancers were identified, 82% of which were invasive. Only 11% of these patients, however, had positive axillary nodes in comparison to the 63% incidence of positive nodes in occult lesions reported by McClow and Williams.[61] Suspicious calcification was the mammographic indication for biopsy in 184 patients. On only two occasions were the calcifications missed at the time of biopsy, and 20% of the biopsy specimens were malignant. These data are compared to results presented in 1982 by Powell et al.[65] who reported 251 consecutive patients with mammographic calcifications as a sole indication for biopsy. Forty-seven breast cancers were identified (19%), of which 36 (77%) were *in situ*. One of 11 invasive cancers had associated axillary nodal metastasis. Of the 106 patients who had a benign diagnosis, only four required subsequent biopsy for calcifications, all of which were benign. Thirty-seven biopsies (13%) would have been inadequate without the use of specimen radiography. Letton[63] also reported a 17% incidence of carcinoma in patients operated upon because of mammographic evidence of suspicious calcifications.

In an evaluation of 10,131 asymptomatic women in the Louisville Breast Cancer Detection Demonstration Project, Bland et al.[66] compiled an analysis in 1981 for 1759 histologic characteristics in biopsies of 863 patients with proliferative and nonproliferative fibrocystic disease. Xeromammography (XM) allowed recognition of ductal and lobular hyperplastic lesions, sclerosing adenosis, or epithelial cysts as the major constituents of 64–69% of the high-risk XM images. However, XM parenchymal patterns observed in these screenees incompletely correlated with known pathologic variables and risk factors. Consequently, the authors recommended clinical integration of risk factors with XM patterns to determine those patients who should be followed at frequent intervals.

In 1976 Baker[67] challenged the necessity of breast biopsies as an inpatient procedure. He reported on 153 consecutive biopsies done on outpatients under local anesthesia. Nineteen breast cancers were detected, and the patients were hospitalized within 1–3 days of biopsy for definitive treatment. Only one patient developed a small hematoma. The author emphasized that there was a tendency to limit the extent of the biopsy if the procedure was done under local anesthesia and that every effort should be made to excise a generous portion of normal breast tissue surrounding the palpable mass.[67] In 1983 Wanebo et al.[68] reported 100 patients on whom a definitive diagnosis was made by fine needle aspiration of a suspicious breast mass by use of a piston syringe with an attached 22-gauge needle. Seventy-one patients had mastectomy without frozen section confirmation of the diagnosis, and all had breast cancer. This presentation stimulated a heated discussion about the advisability of progressing to mastectomy with only fine needle aspiration cytology as the diagnostic criterion. Three SSA members, Zeppa, Newsome, and Horsley each reported one false-positive cytologic diagnosis from their institutions. The summary opinion was that specimens obtained by fine needle aspiration and read by an expert pathologist were satisfactory to progress to mastectomy, yet most surgeons managing breast diseases were not in a position to have the luxury of a pathologist with such expertise.

In 1930 Newsome et al.[69] evaluated the influence of time and sample procurement on estrogen receptor activity. Patients were treated by a modified radical mastectomy from 1 to 7 days after biopsy. Estrogen receptor activity was done both on the initial biopsy specimen and on tumor samples removed from evaluable patients at the time of mastectomy. Changes in estrogen receptor levels ranged between 15% and 100% with a mean decrease of 70% during the interval from biopsy to mastectomy The authors speculated that the decrease in receptor activity was secondary to necrosis, tumor manipulation, hematoma generated from the biopsy, and the anoxic period during the mastectomy. Byrd in discussion said the paper underscored the fallacy of the two-stage procedure. Biopsy with subsequent mastectomy had inherent risks, particularly when done at an institution that did not furnish full pathologic capabilities, such as frozen section diagnosis and an ability to process tissue for proper hormone receptor activity.

In a review of 80 patients in 1984 Kohail et al.[70] made a summary statement that estrogen receptor was most predictive of disease-free survival, whereas lymph node status was more important in predicting overall survival.

In 1971 Davis et al.[71] reported two cases of necrosis of the female breast complicating anticoagulant therapy. In both patients, 4 days after initiating treatment with sodium warfarin (Coumadin), the breast became painful and examination revealed a swollen organ with a bluish discoloration. Bullae appeared rapidly and frank necrosis of the breast with a sharp delineation from surrounding normal tissues soon followed. Simple mastectomy was required for treatment. Etiology of the necrosis is unknown, although it is usually unilateral and cessation of the drug does not reverse the process.

Chemotherapy

Chemotherapy of breast cancer has not been emphasized on programs of the SSA. However, the now famous "one rat" experiment was presented by Ochsner[15] in 1926. He first reported the use of colloidial gold in a patient with inoperable breast cancer and obtained partial remission of local, regional, and distant metastatic disease. There had been criticism that the use of colloidial gold would result in fatty degeneration of the liver. Ochsner placed a rat weighing 154 g on a dose of 0.001 g of colloidial gold daily per os and killed the animal after 4 months. At autopsy, there was no sign of fatty degeneration of the liver.

In 1970 Shingleton et al.[72] reviewed the various multi-institutional chemotherapy protocols in use for mammary cancer. The overall response rate was between 25% and 31%. Early data suggested, however, that a combination of drugs was more effective than single active agents. The best response rates for tumor regression (68%) were achieved with a five-drug combination regimen consisting of cytoxan, prednisone, methotrexate, vincristine, and 5-FU. Also, Shingleton discussed a theoretical advantage of initial ablation of endocrine organs and, after relapse, treating secondarily with multiagent chemotherapy. Interestingly, such sequential treatment had not yet been used extensively. The authors arrived at their conclusion by noting that the survival rates from adrenalectomy and from chemotherapy for patients with bone and soft-tissue metastases were approximately the same and, possibly, the sequential application of these treatments might double the duration of the response.

Bilateral Breast Cancer

In 1971 Finney et al.[73] reported 50 patients with bilateral carcinoma of the breast, 13 of which were synchronous. Demonstrable carcinoma *in situ* contiguous to the invasive lesion was quite common and gross multicentricity occurred in five patients. In 1984 Wanebo et al.[74] again addressed the question of bilaterality of breast cancer and suggested a reduction in risk by biopsy of the contralateral breast at the time of definitive treatment of the initial lesion. Sixty-two patients had contralateral biopsies, and 13 patients (21%) had simultaneous contralateral breast cancer, 11 (18%) of which were occult. Six of the lesions were lobular carcinoma *in situ,* four were intraductal carcinoma, and three were invasive adenocarcinoma. Wanebo et al.[74] presented data to indicate that contralateral invasive breast cancer has a grave prognosis and concluded that contralateral biopsy, by identifying breast cancer at its earliest stage, was indicated when a patient has a documented family history of breast cancer, ipsilateral multicentricity, lobular carcinoma *in situ,* or parenchymal patterns on mammography, which make follow-up study by this technique difficult. This presentation produced heated debate. Myers presented evidence to indicate that bilateral breast cancer did not, by definition, have a poor prognosis, and Sutherland concurred. Bland noted the incidence of synchronous bilateral breast cancer to range from 0.27% to 2%, and if Wanebo et al.[74] were to remove lobular carcinoma *in situ* from their study, the detection of synchronous lesions would be approximately the same as that generally reported.

Breast Reconstruction

Lynch et al.[75] reported 14 patients who had breast reconstruction following mastectomy. The gel prosthesis was utilized and, when flap reconstruction was required, the thoracoepigastric region served as the donor site. The authors recommended reconstruction for any well-motivated patient in whom the surgeon was reasonably assured of having eradicated all disease from the chest wall. The reconstructive procedure should follow complete wound healing and the completion of adjuvant therapy. Georgiade et al.[76] recommended immediate breast reconstruction if the tumor was less than 1 cm in diameter or was documented to be an *in situ* lesion. None of the four local recurrences identified in the 50 patients reported by these authors was masked by the reconstructive procedure. Five patients, on final pathologic evaluation, had unsuspected evidence of nipple–areola involvement. The authors did not, therefore, recommend use of the autologous nipple–areola complex for reconstruction. Hartrampf and Bennett[77] presented their extensive series of 300 patients undergoing breast reconstruction utilizing the transverse abdominal island flap. Complications were minimal and chest wall recurrence developed in five patients within a follow-up period of 7–45 months. In one patient, the reconstruction delayed identification of the recurrence by approximately 3 months.

Summary

The development of current concepts in the treatment of breast diseases during the last 100 years is well documented in the *Transactions of the Southern Surgical Association.* Fellows of the SSA have been on the cutting edge of these developments and chose the SSA as the forum to describe and debate their new observations.

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Abdominal Trauma at the Southern Surgical Association, 1888–1987

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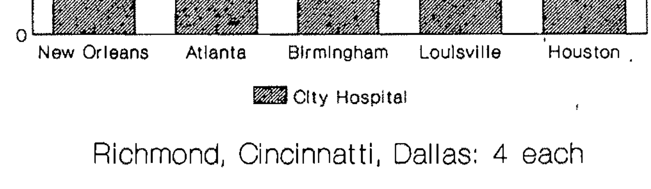
Since 1888 98 papers have been presented to the Southern Surgical Association (SSA) dealing directly or indirectly with abdominal trauma. The papers reflect the progress over the century in the management of this injury. Almost two-thirds of the papers have originated from the major city hospitals of the south. An interest in abdominal trauma has been manifest among the officers of SSA. Twenty-two presidents have presented papers or taken part in discussions. Four 25-year eras were identified. In the earliest, exploration of abdominal wounds was firmly established as a principle. The second period was characterized by consolidation of principles and strengthening of supportive care. The third era encompassing World War II marked a nadir in productivity. In the last 25 years a reawakened interest has resulted in a marked increase in the number and quality of presentations, which have increasingly focused on specific organ injuries.

THE LOVE AFFAIR of the Southern Surgical Association (SSA) with the subject of abdominal trauma began at the first meeting in 1888 and has continued with undiminished ardor to the present day. Ninety-eight papers dealing directly or indirectly with abdominal trauma have been presented and many of these have profoundly influenced the management of trauma as it has been practiced in the United States. The presence of large public teaching hospitals in most of the major southern cities undoubtedly has contributed to the large number of reports that have come out of the South. Institutions such as Charity Hospital in New Orleans, the Hillman Hospital of Birmingham, Grady Hospital in Atlanta, the Louisville General Hospital, Parkland Hospital in Dallas, and the Ben Taub Hospital in Houston have provided the opportunity for young surgical investigators to make important contributions in the study of trauma and, of course, have served as a training ground for innumerable southern surgeons. The importance of these great institutions can hardly be underestimated. Almost two-thirds of the total number of papers on abdominal trauma had their origin in the records of these great institutions (Fig. 1). The New Orleans Charity Hospital, with its 11 papers, may well have had the most single-minded devotion to abdominal trauma. Since 1893 case records of more than 10,000 patients with abdominal injury have been reported in the literature from that institution alone.

The story of abdominal trauma at the SSA may be conveniently divided into four 25 year eras (Table 1). The first, extending from 1888 to 1912, could be characterized as one that defined the role of surgery in the



Richmond, Cincinnatti, Dallas: 4 each

FIG. 1. Contributions on abdominal trauma from major city hospitals. Almost two-thirds of the presentations on abdominal trauma have had their origin in the major city hospitals of the South.

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management of abdominal trauma. The sense of excitement and adventure that permeated the papers and the discussions of that period is almost palpable. The second era, which includes the first World War, was one of consolidation of principles. Attention was focused on individual management of specific lesions and the general support of the patient before and after operation. The third era encompassed World War II and represented the nadir of productivity with only 15 papers presented to the SSA during this period. The Lessons of War appear to have been taken to heart by most surgeons with uncritical enthusiasm and no one seemed willing to question apparently settled issues. The last era has been characterized by the presentation of 33 papers (Fig. 2), many of them reexamining old dogmas, with nothing left sacred. These papers have played an important role in shaping the modern management of abdominal trauma and continue to open new pathways. While presentations of the earlier eras tended to dwell on the general topic of abdominal trauma, the latter era has focused on specific intra-abdominal lesions (Fig. 3).

The enthusiasm of the membership for abdominal trauma has been shared over the years by our officers. Twenty-two of our past presidents have manifested major interests or have presented papers on abdominal trauma at a meeting of the SSA (Fig. 4).

Discovery and Excitement, 1888–1912

The surgical management of abdominal trauma had its origins just prior to the founding of the SSA. Prior to 1880, no formal laparotomies had been performed for gunshot wounds of the abdomen, and during the Civil War (1861–1865) such wounds were managed by expectant therapy. In 1881 the death of President Garfield from an assassin's abdominal gunshot wound focused attention on the possible role of surgery in this lesion. Garfield had been managed without operation, but by 1882 Professor R. A. Kinloch of Charleston (Fig. 5), a founding member of the SSA, had explored a patient and sutured five intestinal wounds. Unfortunately, the patient had seven intestinal wounds and did not survive.[1] This preliminary attempt was followed shortly by Kocher's successful suture of a stomach wound and Bull's successful closure of an intestinal wound (the first in the United States). In 1887 three papers were presented to the American Surgical Association discussing the propriety of laparotomy for gunshot wounds, among them a paper by Kinloch. A long discussion ensued with important contributions from a number of southern surgeons. By the time of the first meeting of the SSA, the utility of laparotomy for penetrating wounds of the abdomen, in particular gunshot wounds,[3,4] was becoming fairly firmly established.

TABLE 1. *Four 25-Year Eras of Abdominal Trauma at the SSA*

1888–1912	Discovery and Excitement
1913–1937	Consolidation
1938–1962	The Lessons of War
1963–1987	Reexamination and Discovery

The first presentation on this topic to the SSA was at the first meeting, by R. M. Cunningham[2] of Pratt Mines, Alabama, who reported on the case of a Scotch miner who had shot himself with a .38 caliber pistol. He was managed expectantly. Eighteen hours later, signs of peritonitis appeared and the patient died at 52 hours.

The following year, two papers were presented in tandem, dealing with anastomotic techniques for the small bowel. Much of the discussion of these two papers was in the context of the application of these techniques to the management of gunshot wounds. The general tenor of the discussion that followed was that laparotomy should be strongly considered for patients with penetrating gunshot wounds. President Hunter H. McGuire (Fig. 6) of Richmond was perhaps most succinct in reminiscing about his days as a military surgeon in the Civil War: "I look back with horror on the days of the war when I practiced surgery on gunshot wounds to the abdomen. We gave them opium, etc. and waited until they died. Now a man has no right to do this."[5]

Four years later, at the meeting in New Orleans, W. F. Westmoreland of Atlanta came down on the side of laparotomy in his paper on the treatment of gunshot wounds.[6] Westmoreland seemed particularly incensed about some of his less radical colleagues: "The physician calls in the abdominal surgeon and, although he expresses himself very radically about operations involving the removal of ovaries and tubes, when he comes to these cases [abdominal trauma] it is *opium and wait.*

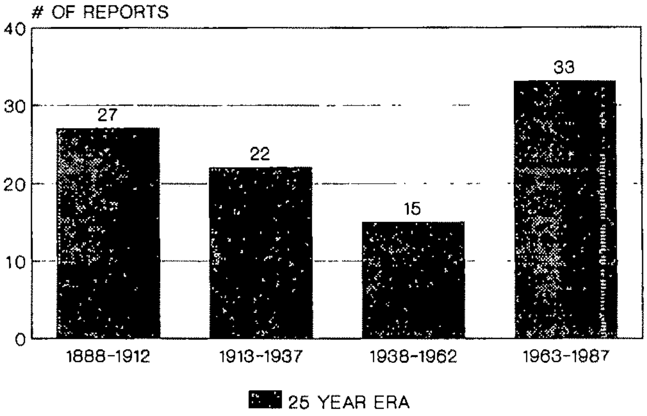

FIG. 2. Papers presented to the SSA by 25-year eras. A nadir of productivity was reached following WW II, but in recent years, there has been a vigorous reawakening of interest with a marked increase in the number and quality of presentations.

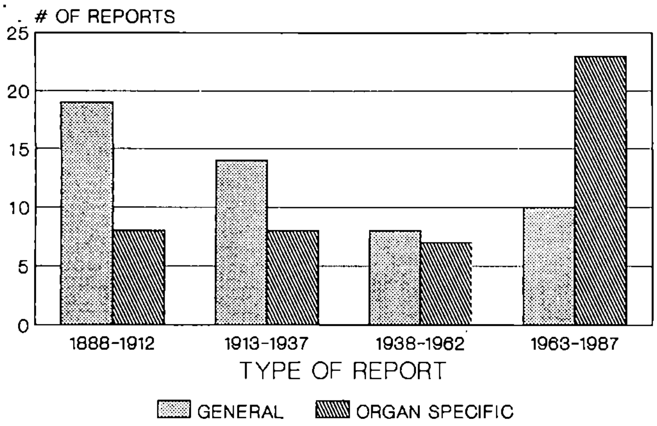

FIG. 3. General *versus* organ-specific reports on abdominal trauma (by era). In recent years an increasing proportion of papers has focused on specific organ injuries. In the earliest era general papers on the suitability of laparotomy dominated the discussions.

When he comes to the bedside and sees the case before him, he does not have the courage of the convictions he has so openly avowed. Particularly, this is true of those gynaecologists and coeliotomists who, like toadstools, spring up in a night." Westmoreland was supported in his views by A. B. Miles of New Orleans, Cunningham of Alabama, and J. McF. Gaston of Atlanta, but J. D. S. Davis of Birmingham expressed some caution about routine laparotomy.[7]

Papers by Tiffany of Baltimore in 1894,[8] and by Bradford Brown of Alexandria in 1895[9] continued the colloquy, climaxed by the paper of W. E. Parker of New Orleans, Louisiana at the meeting in Nashville in 1896.[10] Parker reported on 13 personal cases operated upon at Charity Hospital, New Orleans of whom six survived. He provided an extensive summary of the world's literature on the management of bullet wounds to the abdomen published to that date, and provided excellent descriptions on how to manage individual lesions. Parker's paper provoked a long, excited discussion with the vast majority of the individuals strongly supporting an aggressive employment of laparotomy in the management of gunshot wounds.

1888-1912

WD Haggard
HH McGuire
*B Brown
*LM Tiffany
WEB Davis
*FW McRae
HA Kelly
FW Parham
*WO Roberts
R Matas

1913-1962

*JY Brown
A Singleton
A Ochsner
JD Rives

1963-1987

*JD Martin
*H Wilson
*JD Rives
*RS Sparkman
*WD Warren
*I Cohn, jr
A Mansberger
JL Sawyers

FIG. 4. A list of the presidents of the SSA who manifested major interests in abdominal trauma. *Made presentation on trauma at an annual meeting of the SSA.

Finally, Howard A. Kelly of Baltimore rose and made the following proposal: "Would it not be well, Mr. President, in view of the serious medico-legal complications that arise in these cases, to pass a resolution favoring immediate operative interference whenever any of us come in contact with these cases? I, therefore, offer the following: Resolved, that it is the sense of the members of the Southern Surgical and Gynecological Association that in gunshot wounds penetrating the abdominal cavity the proper routine procedure is to make an immediate exploratory incision. Seconded and carried."

One can almost picture Parker being carried from the auditorium on the shoulders of his cheering fellow members! His high standing among his colleagues was to be short-lived.

Two years later Parker returned to the speaker's podium with another paper.[11] In the interim, he had served as a surgeon with the American military forces in Cuba. Parker had entered the conflict with the intention of exploring patients who sustained abdominal wounds, but soon found "surgery with troops in the field is a very different thing from surgery in civil life."[11] He concluded, "Wounds of the abdomen healed without operative interference. When I saw the conditions I strongly advised against surgical management."[11] He had discovered that exploration of abdominal wounds in a military field hospital was too dangerous. His conclusion, it should be stated, was shared by most of the other physicians who had participated in the Cuban expedition and by virtually the entire military surgical establishment. Yet Parker's recantation of his advocacy of laparotomy for penetrating abdominal wounds did not sit well with his audience. One after another of his fellow members rose and denounced him. H. H. Grant of Louisville, who had presented a paper recommending laparotomy for all gunshot wounds,[13] said, "Some of the statements by Dr. Parker are unquestionably astonishing." F. W. McRae[14] from Atlanta had reported on the recent experience at Grady Hospital and reiterated his firm conviction that every case of penetrating wound of the abdomen "where there is reasonable doubt as to injury of the abdominal viscera should be subjected, at least, to an exploratory operation." One or two faint voices were raised in support of Parker, but the discussion continued with a reiteration of Kelly's resolution from the 1896 meeting and the accusation that Parker was advising "masterly inactivity."[2] Westmoreland went further: "It's not 'masterly inactivity,' it is '*criminal inactivity.*' " Parker, in fact, had not changed his position on civilian gunshot wounds. He still advocated exploration for these lesions.

Grant was so incensed that the next year he presented another paper continuing his denunciation of Parker and concluding "With these facts before us, it is clear that to delay, in a delusive hope, until peritonitis shows its folly is almost a crime. The practical management of a suspected penetrating wound is as plain a duty as the tying of a bleeding artery. As soon as possible after injury, the patient is to be transported to a suitable place [and explored]."[15] And lest there be any doubt about how he stood about Parker's recommendations: "Because a man falls out of a balloon from a considerable height . . . without sustaining injury is that any reason why we should encourage others to undertake similar experiences?"

Undaunted, Parker stood his ground saying that he had not operated on a gunshot wound to the abdomen for about 3 years and reiterating the firmly held belief by the military that operations in the field could not be performed safely. (This conclusion of the military surgeons, shared by the British, continued until 1915.)

Another dozen papers over the ensuing years[16–23] continued the argument with ill-tempered comments about the military surgeons and about Parker continuing until 1915. The most important of these subsequent papers was that of E. D. Fenner[17] of New Orleans who updated the Charity statistics presenting 152 cases (which was a larger series than that experienced by the army during the Spanish American War). Parker, in the meantime, resigned from the SSA and retreated to Hot Springs, Arkansas.

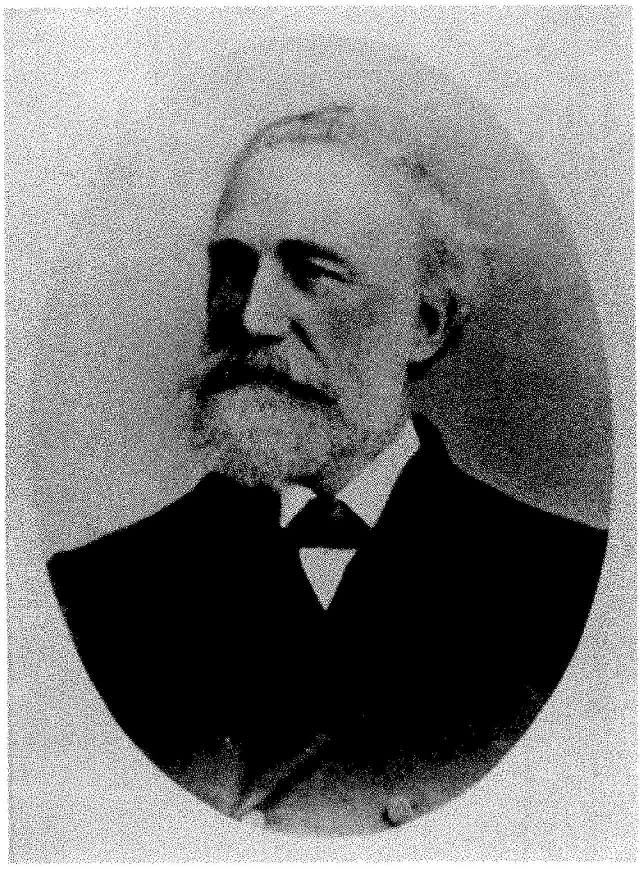

FIG. 5. Professor R. A. Kinloch of Charleston, a founding member of the Southern Surgical and Gynaecological Association. He was the first American to explore a patient with a gunshot wound of the abdomen.

FIG. 6. Hunter H. McGuire of Richmond, a founding member of the SSA and an early proponent of laparotomy for trauma. He had served as Stonewall Jackson's surgeon and was perhaps the most respected and influential trauma surgeon of his day.

An interesting sidelight of this era was the formidable presence of Nicholas Senn. Senn was elected to membership of the SSA in 1893 and was a member until he resigned in 1905. No evidence could be found that he actually attended a meeting, but the rise and fall of his influence at the meetings makes an interesting story.

Senn was perhaps the most prolific intestinal surgeon of his era, with a deep interest in abdominal trauma. He had developed a variety of techniques of intestinal anastomosis, had invented the Nicholas Senn hydrogen gas insufflation test for diagnosis of abdominal visceral penetration,[24] and was the founder of the Association of Military Surgeons (Fig. 7). Senn's hydrogen gas test consisted of insufflating hydrogen through a tube in-

FIG. 7. Nicholas Senn of Milwaukee, a prolific student of abdominal trauma whose presence was very much felt during discussions of abdominal trauma in the first decade, founder of the Association of Military Surgeons.

serted into the anus of a wounded patient. The patient was then examined for abdominal distention and tympani. A lighted taper was placed near the wound of entrance. A small explosion accompanied by a flaring blue flame was a positive test, indicating penetration of the intestines. The value of this test was stressed by Cunningham in his first paper on abdominal trauma in 1888 when he expressed his opinion that the Senn test would have made the diagnosis in his patient and led him to earlier exploration.[2] The papers on intestinal anastomosis the following year paid tribute to Senn's seminal contributions in intestinal anastomosis.[3,4] There were repeated favorable references, both to the hydrogen gas test and to Senn's contributions in these papers and in the discussion which followed. McGuire was typical: "I think the whole profession is greatly indebted to Dr. Senn" and J. D. Davis emphatically said: "I don't open up the abdomen when I have the hydrogen gas with me until I have used it." Senn's ascendency continued through Parker's presentation of 1896,[10] but when Senn supported Parker's views about the management of abdominal wounds in the military,[25] he might as well have written his epitaph. By the next year, Grant was calling the Senn test "worse than useless." McRae went further: "the gas test of Senn is worse than useless. It is dangerous" And W. E. B. Davis, who in previous years had made complimentary remarks about Senn, was moved to say, "Dr. Senn's influence has been harmful. Every Community has suffered from his writings." Senn's opinions and writings disappeared from the transactions and no further favorable reference to him can be found. Senn's name does not appear in any subsequent discussions. He resigned in 1905, whether or not at the instigation of the council is not recorded. It is notable that in a presentation celebrating the 50th anniversary of the SSA, Hubert Royster spoke as if Senn had actually attended a meeting. This is strong evidence of his forceful influence.

Seventy-five years later, a young perhaps foolish member* had the temerity to advocate again "masterly inactivity" in the management of gunshot wounds of the abdomen.[26] Perhaps, if he had known at that time the fate of Parker and Senn he would have been more cautious!

Consolidation, 1913–1937

This era was marked by considerably more civility in the discussions about abdominal trauma. Just prior to the beginning of this era, W. D. Roberts of Louisville had given a presidential address on Southern Surgeons, reminding his audience that he himself had performed the first successful exploration of a stab wound in 1884.[27] John W. Brown's presidential address of 1913 was a superbly comprehensive paper on the management of acute abdominal conditions, including abdominal trauma.[28]

With the coming of the World War, there was a renewal of interest in the military aspects of trauma. The 1914 meeting had three papers dealing with military surgery.[29] The paper of H. D. Marcy of Boston paper was an affectionate reminiscence, 50 years later, of his experiences as a young military surgeon in the Yankee Army during the occupation of Charleston, South Carolina.[30] His description of the hardships endured by the Yankee soldiers apparently fell on deaf ears and the paper was not discussed. Colonel Charles Richard of the U.S. Army, a guest speaker, reiterated the military's continuing position that formal exploration of the abdomen for penetrating gunshot wounds should not be undertaken unless there was evidence of uncontrolled hemorrhage.[31] This position of military surgeons still rankled and Colonel Richard was subjected to pointed questioning during the discussion. The members of the SSA were, of course, right on this issue and the military abandoned its position shortly following the start of the war.

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* The author is referring to his own epochal work in this field (Ed).

W. L. Haggard of Nashville was moved to wax patriotic in his presidential address of 1917.[32] C. H. Peck of New York returned from the front in 1918 to describe the treatment of war wounds in the hospitals of the expeditionary forces.[33] The 1920s brought a focus of interest in improving the supportive care of patients with abdominal injuries. A. M. Willis of Richmond reported on some clinical and experimental observations in the use of saline irrigations in diffuse peritonitis due to trauma.[34] Mason presented a paper on the influence of hemorrhage in the mortality of gunshot wounds of the abdomen.[35] Mason and the program committee were so impressed by this paper that he gave a second one with the same title the following year.[36] Mason divided his series into two groups, a large hemorrhage group of patients, and a small hemorrhage group. The large hemorrhage group had a mortality rate of 90%, whereas the small hemorrhage group had a mortality rate of only 30%. He concluded that hemorrhage was an important factor in the mortality rates of these patients and strongly advised the use of blood transfusions, a conclusion that was supported by many of the discussants.

Later in the era, there occurred a brief infatuation with shotgun wounds of the abdomen, beginning with the report of G. H. Bunch, of Columbia in 1928[37] of four patients who sustained close-range shotgun wounds; three died. Of three with long range shotgun blasts, two died. Bunch advocated early exploration, a position seconded by most of his discussants. Mason was back again during the discussion giving a minipaper reiterating the increase in mortality associated with hemorrhage in gun shot wounds of the abdomen.

Willis[38,39] followed Bunch's paper in 1931 with a report on penetrating wounds of the abdomen from pistol, rifle, and shotgun missiles and emphasized that long-range shotgun wounds with scattered shots could be managed nonoperatively, a position he soon supported with a paper in 1934 reporting a series of animals wounded with long-range shotgun blasts in which more than one-half of the animals survived without operation. Willis' 1931 report was also notable: 63 cases, all treated in the tiny hamlet of Rocky Mount, North Carolina. L. H. Landry, from New Orleans, in discussing Willis' paper, brought the audience up to date on recent Charity Hospital statistics, which included a total of 3141 gunshot injuries treated from 1914 to 1924.[40]

Perhaps the most important major presentation from this era was that of Heuer[41] who reported on 7000 cases of major trauma seen at the Cincinnati General Hospital, among which there were 334 patients with abdominal injury treated with a mortality rate of 50% for gunshots and 13.2% for stabs. This paper stimulated a general discussion on the importance of establishing trauma as a specialty and the need for establishment of special training in trauma surgery.

The Lessons of War, 1937–1962

The war in Europe had begun when Storck[42] presented his paper on penetrating wounds of the abdomen. It was a series of 46 cases operated on personally, with a mortality rate of only 40% among the gunshot wounds. This very long, impressively documented paper extensively described the proper management of penetrating wounds of the abdomen and served as the basis for his manual on the management of abdominal trauma, which became an official army document. The following year, with war raging in Europe, a symposium on war injuries was given, with Storck[43] again making the presentation on abdominal wounds. During the war, there were papers by M. E. DeBakey and B. N. Carter[44] on war surgery, DeBakey and F. A. Simeone[45] on vascular injuries, and Lt. Col. L. G. Lewis[46] on pelvic injury, a remarkably small output considering the number of surgeons who participated in the war. In the early post-war period, there was a marked drop-off of interest in trauma, perhaps reflecting a general conviction that war surgery had provided all of the answers for the management of abdominal trauma. This view clearly was reflected in the paper of D. H. Poer of Atlanta in 1947, which strongly recommended applying military surgical principles to civilian trauma.[47]

The era closed with an important paper by Wilson and Sherman.[49] This presentation was a harbinger of things to come in a later era and set the stage by raising questions about the appropriateness of universal application of military principles to civilian trauma.

Only 15 papers were presented during this era, representing a nadir of interest and productivity perhaps reflecting a post-war attitude that all of the important issues had been answered.

Reexamination and Discovery, 1963–1987

The most recent era has been characterized by a marked increase in the interest in the general subject of abdominal trauma and a focus on the more specialized aspects of specific organ injury. Heated discussions, new ideas, and a willingness to challenge old precepts returned in full force to the forum of the SSA. J. E. Pridgen's[50] presentation in 1966 on penetrating wounds of the abdomen reported on 776 cases from the University of Texas in San Antonio and provoked discussions on the advisability of exploration for stab wounds. F. C. Nance's[26] paper in 1973 extended this discussion. By this time, the concept of selective management of stab wounds was being grudgingly accepted in a number of trauma institutions, but Nance's inclusion of gunshot wounds as candidates for selective nonoperative management was greeted with deep suspicion, if not hostility. The discussion was continued in 1983 when W. C. Lee, J. F. Uddo, and Nance presented the Charity Hospital experience with selective management of stab wound reiterating the conviction of the LSU group in New Orleans that clinical criteria alone were sufficient to decide whether or not a patient with a stab wound needed exploration. These authors reported a negative laparotomy rate of 7.8% and a mortality rate of 2.2%. One death from inappropriate application of their protocol was acknowledged.[51] D. V. Feliciano of Houston, in discussing this paper, reiterated the reliance at Ben Taub Hospital on local wound exploration, a policy also followed by L. M. Flint Jr. in Louisville. A. V. Donovan of Los Angeles supported the authors, saying that clinical criteria were utilized in Los Angeles in the evaluation of patients.

Specific Organ Injuries

An important aspect of the bibliography of abdominal trauma of the SSA has been the papers that have focused on specific organ injuries. As laparotomy became firmly established, a concentration on management of individual lesions became inevitable. The trend has become much more pronounced as very large series of patients from the major trauma centers became the subject of comprehensive study.

Diaphragm

Three case reports constitute the total discussion of diaphragmatic injuries at the SSA. The first report was given in 1904 on a patient who had sustained gangrenous changes to the bowel; the patient died.[52] The other two cases were patients diagnosed 6 and 7 weeks postinjury in whom successful elective repairs had been accomplished.[53,54] All of the authors emphasized the difficulty in making the diagnosis of ruptured diaphragm (which is perhaps understandable because in all of the case reports the diagnosis had been delayed).

Vascular

Past presentations on vascular injuries have been made nine times beginning with LaRoque's report of an A-V fistula following a bullet wound to the external iliac artery and vein that he managed by ligation of both vessels.[55] The patient and his extremity survived. In describing his concern about the vascular supply to the leg, G. P. LaRoque of Richmond comments that a week after the operation, "I took the liberty of sticking a pin in his toe to see if it would bleed. It bled."[55] LaRoque finished his paper by including a thorough review of the available literature on the lesion, paying tribute in particular to the contributions of Halsted and Matas. LaRoque returned the next year with another paper.[56] At least LaRoque had the modesty to quote a "distinguished American surgeon" as having "prayed to be delivered in time of illness from the care of a doctor who has had *a* case. Might he not with equal fervency pray to be delivered from the surgeon who's opinions are firmly fixed after the successful management of *another* case."[56] This patient was also treated by ligation and survived with an intact leg.

In 1928, an aortic injury was reported by J. G. Sherrill of Louisville in a patient who sustained severe blunt trauma. He developed a thrombosis of the distal aorta. Sherrill had attempted thrombectomy but, unfortunately, his patient did not survive.[57] He was congratulated for his courage by the members during the discussion.

The modern papers on vascular injury began with DeBakey and Simeone's review of arterial injuries encountered during World War II, presented at the meeting in 1945.[45] This classic presentation reviewed 2471 cases of arterial injury and has served as a milestone for all subsequent reports on arterial injuries. The paper included a discussion of 47 intra-abdominal arterial injuries.

Most other presentations on arterial injuries have dealt in passing with the abdominal vessels. The presentation of Hardy et al.[58] in 1974 described their experience in Jackson with 22 abdominal aortic and 44 other abdominal vessels among 360 arterial injuries. Reynolds et al. reviewed 20 abdominal vessels among 191 patients with arterial injuries.[59] Feliciano et al.[60] reported on 408 patients with vascular injuries seen in 1 year, among them being 130 patients with abdominal arterial injuries. Many of the patients in this series were treated with prosthetic bypass or insertion of a venous conduit.

McCune et al.[61] dealt with the specialized problem of mesenteric thrombosis following blunt trauma. They emphasized the high mortality rate associated with the lesion, having observed three deaths among the four reported cases.

In 1974 Mattox et al.[62] presented a series of 22 patients with injury to the portal vein of whom 11 survived. The authors recommended lateral repair, end-to-end anastomosis, or portacaval shunt because ligation was associated with a 100% mortality rate.

The consensus of opinion regarding vascular injuries to the major abdominal vessels revolves around the need for early diagnosis and control of hemorrhage. Virtually all reports and discussion confirm the need for direct arterial repair and/or anastomosis where feasible, or insertion of a variety of prostheses where primary repair is not possible.

Urology

Six presentations before the SSA have dealt with trauma to the urogenital tract. Two papers presented in successive years, 1917 and 1918, reported on injuries to the kidney. J. M. Mason's paper reviewed the literature and presented three cases.[63] Mason and the majority of the discussants of the paper favored nephrectomy or suture of the injury.[63] There was considerable discussion about the virtues of suture with a general consensus that the kidney should be preserved if possible. The following year, S. G. Ledbetter[64] also presented a case of kidney rupture treated by suture with survival, and in the discussion, T. S. Cullen, among others, strongly supported his view.

Wounds of the urinary bladder were first discussed by R. Douglas of Nashville in 1893.[65] He described a patient who had had a bladder ruptured by the shaft of a buggy. After determining that it was an extraperitoneal injury, Douglas managed the patient by simple drainage apparently without a bladder catheter; the patient recovered fully.

Other papers have dealt with bladder injuries associated with pelvic fractures.[66] In 1944, a guest speaker, Lt. Col. L. G. Lewis[46] described four severe war injuries and W. L. Weems of Jackson[67] discussed a series of 86 GU injuries identified in 282 patients with pelvic fractures. Both authors recommended suprapubic cystostomy through a small lower abdominal transverse incision with appropriate drainage. Weems' paper made an excellent case for delayed repair of urogenital lesions, relying initially on suprapubic cystostomy and drainage and making a formal repair at a later time.

Pelvis

Only one paper over the years has dealt specifically with pelvic injuries, that of Flint et al.[68] of Louisville, which was presented in 1978. (Two other papers dealing with the pelvis focused on genitourinary injuries.) Flint's paper defined a subgroup of patients with pelvic fractures who had severe extraperitoneal hemorrhage and described the use of a G-suit with inflation to control hemorrhage from this severe complication. One of their patients was managed by angiography, a method that might well be regarded as the method of choice at the present time.[68]

Spleen

Four papers on splenic trauma have been presented to the SSA. They reflected the cyclic evolution of the management of splenic trauma over the past century. Tiffany's presentation in 1894 discussed a patient with a gunshot wound of the spleen managed by suture. The tenor of the discussion was that splenic trauma could be managed either by suture or splenectomy.[8]

W. P. Carr's presentation in 1906 also described management of splenic trauma by suture or splenectomy, but Carr recommended a splenorrhaphy only for "injuries that can be safely repaired."[69] By 1917, A. M. Willis of Richmond was advocating splenectomy for all splenic trauma.[34] This rather rigid approach continued and was epitomized by the discussion of J. H. Morton's paper on blunt trauma in 1956 in which one of the members stated "the treatment for ruptured spleen is, of course, splenectomy."[70]

The report in 1952 by King and Shumacker[71] first called attention to the risk of overwhelming infection following splenectomy in infancy. Subsequently, other reports led to a reevaluation of the management of splenic trauma. A history of this reevaluation was summarized by R. T. Sherman of Tampa in 1980.[72]

By 1984 Feliciano et al.[73] presented a series of 305 patients with splenic injury managed by selective splenorrhaphy and splenectomy. Forty-five percent of the patients had splenorrhaphy and 55% of the patients had splenectomy; they concluded that splenectomy would be generally required in patients with multiple associated intra-abdominal injuries and the more severe grades of splenic injuries and that splenorrhaphy could be performed in patients with a smaller number of associated intra-abdominal injuries and less severe grades of splenic injury.[73]

The operative management of splenic injury had thus come full circle to the point where it existed in 1894, namely, splenic injuries are treated selectively, either by suture when possible, splenectomy, or by nonoperative management.

Liver

Martin's presentation in 1946 marked the first time that a paper dealing specifically with wounds to the liver had been given to the SSA.[74] Martin's paper dealt with an experimental injury inflicted to dog livers by hitting each liver 50 times. He reported that hemorrhage following this type of injury could be controlled by packing and debridement.[74] Discussion included a comment by DeBakey reporting on his war experiences with liver trauma and emphasizing external drainage and control of shock.

Sparkman and Fogelman[75] of Dallas presented a summarized series of liver trauma patients from the Parkland Hospital in 1953. The series was subsequently updated by Trunkey et al.[76] in 1973; 811 patients were managed primarily by suture and drainage. However, almost 6% of the total were managed by major resection. A subsequent report by Flint et al.,[77] and the discussion following it, reiterated the importance of less aggressive treatment of hepatic injuries utilizing hepatic artery ligation, selective debridement, drainage, and packing.

Sandblom et al.[78] presented an experimental study in 1975 on healing of liver wounds, demonstrating that the presence of bile greatly slowed the rate of healing of liver wounds.

The paper presented by Busuttil et al.[79] in 1979 dealt with extrahepatic injuries to the portahepatis, including bile duct and portal vein injuries. A total of 28 patients was presented with a variety of repairs recommended as would be expected in this diverse group of injuries.

The most recent paper, that of Pachter et al.[80] emphasized the use of finger fracture technique to allow local control of hemorrhage from hepatic injuries. This paper reiterated the more modern view that these injuries should be treated selectively with minimal reliance on major resections. The discussion that followed emphasized the use of packing in patients with massive hepatic hemorrhage.

The presentations on hepatic trauma at the SSA have reflected changes in attitude that have evolved since 1945. In the 1950s and 1960s there was enthusiasm for aggressive approach to hepatic trauma utilizing major resections. This has gradually changed to one that calls for minimal debridement of necrotic tissue and simple repair by any means that will effectively control hemorrhage. A brief interest in hepatic artery ligation and in common duct drainage appears to have been abandoned by most recent authors.

Pancreas and Duodenum

The first presentation dealing specifically with injuries to the duodenum and pancreas was not made until 1963, which is perhaps understandable considering the complexity of pancreatic and duodenal trauma. Moore and Erlandson dealt with intramural duodenal hematoma.[81] They presented two cases and reviewed 33 others in the literature. Surprisingly, they made no mention of conservative, nonoperative, treatment, nor did they make any mention of of serosal incision as a method of management of duodenal hematoma. These issues, however, were brought up during the discussion and by the time of a second presentation on the same subject by Fuller et al.,[82] nonoperative management in selected patients had become well established and was recommended.

Barnett et al.[83] reviewed the experience of the University of Mississippi in the management of pancreatic injury yielding an overall mortality rate of 13%. Barnett's group relied primarily on drainage. One-third of the 18 patients were treated by distal pancreatectomy and drainage; only one death had occurred.

Several groups have presented large series of patients with duodenal, pancreatic, or combined injuries. The recommended therapies have generated significant controversy in the discussions that followed the presentations. Flint,[84] in discussing duodenal injury, recommended tube decompression of the duodenum through an enterotomy stating that no duodenal fistulas had been observed in any of the ten patients so treated. The majority of duodenal injury patients were treated by suture with a few being treated by other means, such as anastomosis, pancreaticoduodenectomy or duodenojejunostomy.

Jone's report[85] emphasized his preference for anastomosing a Roux-en-Y limb of jejunum to the injured pancreas, which he had employed in 38 of his 274 patients. Drainage alone, either by Penrose or sump, was performed in 197 of the 274 patients.

The presentation by Feliciano et al.[86] emphasized their preference for "duodenal diverticulization" in which the pylorus is closed by absorbable or nonabsorbable sutures and a proximal gastrojejunostomy is constructed. This method was utilized in 68 of 129 patients with combined pancreaticoduodenal injuries. In discussions following this paper, H. H. Stone from Grady Hospital in Atlanta emphasized his preference for triple intubation (gastrostomy, jejunostomy tube extending proximally into the duodenum, and jejunostomy tube extending distally into jejunum for feeding) and F. C. Nance expressed his discomfort with all of these methods, preferring simple reliance on sump drainage, distal pancreatic resection, and occasional pancreaticoduodenectomy.

The controversy over the role of pancreacticoduodenectomy for trauma raised in other forums has seldom been a cause for discussion at the SSA. Salaam et al.[97] reviewed four patients who had been followed 3 years after surviving Whipple procedures for trauma and reported that all were biochemically and physiologically normal. Most large series have included a few patients who were managed by pancreaticoduodenectomy with mortality rates ranging from 20% to 40%.

It seems clear that the management of pancreatic and duodenal injuries is in a state of flux and will be a continuing subject of discussion at future meetings of the SSA.

Esophagus, Stomach, Small Bowel and Colon

There have been ten papers over the years that have dealt with wounds of the hollow viscera. Symbas et al.[87]

report in 1979 included seven patients, among 48 with esophageal injuries who had gunshot wounds of the abdominal esophagus. Four patients were managed by primary repair, or by repair and plication with survival and no sequelae. Two patients had exteriorization of the esophagus because of the extensive injury. These two patients also survived. Symbas et al.[87] recommended early exploration with primary repair of the esophageal wound and plication with adjacent serosa if possible.

W. M. Jordan's report from Birmingham in 1904[88] was the only one to deal solely with stomach injuries. He reported two patients, one of whom had survived. He recommended purse string suture of the stomach wound and appropriately advised searching for the wound of exit in the retrogastric space.[88]

At the second meeting of the SSA, in 1889, two major papers on intestinal anastomosis based on experimental studies were presented.[3,4] Both dealt extensively with repair of small bowel injuries following penetrating trauma. Davis had done an experimental study utilizing a catgut mat as partial support of the anastomosis. A. V. L. Brokaw from St. Louis, presented a series of experiments utilizing rubber rings. Both authors made it clear that the utility of these techniques was primarily for penetrating trauma to the gut. An extensive discussion of both papers followed, including comments by Hunter McGuire of Richmond (perhaps the most respected trauma surgeon of his day), W. O. Roberts of Louisville, and W. E. B. Davis of Birmingham. A striking feature of both the presentations and the discussion is the repeated reference to Nicholas Senn and his pioneering efforts in developing anastomotic techniques. Both Davis and Brokaw acknowledged Senn's contributions in their papers and in their closing remarks.

Three other papers dealing with intestinal injury took the form of case reports. The most notable of these papers was that of A. B. Miles[89] of the New Orleans Charity Hospital wherein lies an interesting story (Fig. 8). Miles reported on a patient who shot himself while carelessly handling his own pistol. The Charity Hospital ambulance brought him to the hospital and he was on the operating table within a half hour of injury. Sixteen small bowel lacerations and three mesenteric wounds were identified and repaired by suture. He made an essentially uneventful recovery. Miles first reported this case to the SSA in 1890. As a young professor of surgery at Tulane, he was undoubtedly aware of the need to publish or perish and this case report appeared in no fewer than four additional publications. Moreover, the patient was mentioned on at least four subsequent occasions during meetings of the SSA. In 1907 during a clinical visit to Charity Hospital, the members of the SSA were given the opportunity to meet the sturdy survivor some 18 years after his injury!

The SSA has had three important presentations on colonic injury, all subsequent to 1970. During World War II, mandatory colostomy for all colonic injuries, no matter how trivial, had been introduced as a method of therapy and had been largely credited for the improvement in survival noted among patients who sustained injuries to the colon. The principle of mandatory colostomy was enthusiastically adapted to civilian practice and became firmly ingrained in clinical protocols at major trauma institutions.

FIG. 8. A. B. Miles of New Orleans, an early vigorous participant in the discussions on abdominal trauma until his untimely death in 1893 at the age of 42.

The enthusiasm for the use of colostomy for all colonic injuries continued despite a number of reports beginning with that of Woodhall and Ochsner[90] suggesting that many civilian colonic injuries could be more safely managed by primary suture repair. These reports had little impact on surgical practice.

The 1971 paper by Beall et al.[91] continued a series of reports from Houston strongly endorsing selective employment of primary suture for colonic injury. This was followed in 1981 by Flint et al.,[92] who strongly endorsed selective utilization of primary suture.[92] In a discussion of this last paper, Harlan H. Stone's prospective study on colon injury was favorably commented upon and a number of the discussants strongly advocated a wider application of primary suture for colonic injury.

The most recent paper presented by Burch et al.[93] in 1985 was a further update of the Houston series, continuing to reiterate the virtues of selective employment of primary suture. These three papers, and others in the recent trauma literature, have served to modify slowly the approach away from the army's mandatory colostomy for all injury towards a more selective approach to colonic trauma.

Blunt Trauma

Four papers have dealt specifically with blunt trauma, although many others have included patients who sustained nonpenetrating injury. Landry's paper in 1934 on football injuries included eight patients who had experienced hematuria, two of whom required nephrectomy.[94] In 1938, F. W. Baily[95] of St. Petersburg presented 100 cases in whom a 34% mortality rate had occurred. The majority of patients were transportation injuries. In 1956, Morton et al.[48] reported on 120 cases treated in Rochester, NY. The most commonly injured organ was the spleen, which these authors felt should be routinely managed by splenectomy. Davis et al.[96] reviewed 437 patients from the Charity Hospital in 1975. A mortality rate of 13.3% was observed, mostly in patients with concomitant head injury. Clinical criteria for evaluation were recommended.

Summary

One cannot come away from a reading of these 98 papers without acquiring a sense of the gusto, enthusiasm, and downright enjoyment that the members of the SSA have had in wrestling with the topic of abdominal trauma. Discussions have been spirited and tough, occasionally boisterous, but usually gentlemanly. New ideas have been presented and challenged, accepted, or rejected. Young men have questioned long-held established principles, and older men have freely shared their wisdom. As a result, the forum of the SSA has been one of the important sources of progress in the field of trauma management. Members of the SSA may be perhaps forgiven if they concur with one of their former presidents, F. W. McRae of Atlanta, who in 1908 said: "When the history of gunshot wounds of the abdomen shall have been written, chief credit must be given to Southern surgeons. Most of the papers on this subject that are worthwhile have been written by fellows of this Association and have been printed in its Transactions."[22]

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Gastroduodenal Ulcer

Overview of 150 Papers Presented Before the Southern Surgical Association 1888–1986

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THE SOUTHERN SURGICAL AND GYNECOLOGICAL ASSOCIATION was formed in Birmingham, Alabama, October 12, 1887. The first scientific session was held in Birmingham the following year on December 4–6. Forty-one charter members were in attendance along with 50 visitors.

This presentation is an overview highlighting some of the important contributions in the surgical treatment of gastroduodenal ulcer disease and its complications by members of the association. A total of 150 papers were presented on this subject from 1888 through 1986. Many important reports cannot be mentioned in this brief review. Emphasis will be placed on the changing patterns of the surgical treatment of ulcer disease that have occurred throughout the years as reflected in the papers by members of the association.

The inaugural presidential address in 1888 was delivered by W. D. Haggard, Sr., of Nashville (Fig. 1). Haggard praised the founding of the association, and in eloquent language outlined the aims and goals for its future in American surgery. He also cited the outstanding accomplishments of two deceased southern surgeons, J. Marion Sims and Ephraim McDowell.

After the presidential address, it is of interest that the first scientific presentation was related to gastric surgery. William Boddie Rogers of Memphis reported on "The Operation of Gastrostomy with a Report of a Successful Case" (Fig. 2). Rogers was a native of Tennessee who had attended Vanderbilt University and graduated from Bellevue Medical College. He later became Professor of Principles and Practice of Surgery at the Memphis Hospital Medical College in 1886, and was later Dean of that institution. He maintained both of these positions until the Memphis Medical College merged with the University of Tennessee in 1913.

Rogers described a gastrostomy performed on a 24-year-old man with an extensive esophageal stricture which followed the ingestion of lye. The operation was carried out under chloroform anesthesia, and the anterior wall of the stomach was sutured to the anterior abdominal wall. On the 10th postoperative day after adhesions had sufficiently sealed the opposing gastric and abdominal walls, a permanent opening was made in the stomach for feeding purposes. The patient was allowed out of bed on the 14th postoperative day and was discharged in good condition on the 26th postoperative day. Although gastrostomy had originally been suggested in 1837 by Egeberg, the Norwegian military surgeon, it had never met with real success until the report of Sidney Jones of London in 1876. Both D. Hayes Agnew and Samuel D. Gross of Philadelphia decried the operation because it was associated with a high morbidity and mortality even in 1878. The report by Rogers represented a real landmark, and he advocated the operation not only for benign esophageal stricture but also for extensive esophageal malignancies. It is of interest that Rogers presented the patient in person before the association. Rogers believed that the high recorded mortality rate could be explained in part by the procedure being done by inexperienced surgeons.

For the next 15 years no presentation addressed the topic of gastroduodenal ulcer. Numerous papers were presented on the manifestations and treatment of ap-

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pendicitis, pelvic infections, pelvic tumors, treatment of fractures, bone tumors, removal of bladder stones, prostatic operations, and ligation of blood vessels.

From 1903 through the 1930s, a group of interesting papers on gastroduodenal ulcer were given. Simple gastrojejunostomy was mainly the operation of choice for both duodenal and gastric ulcer during the early years and was also advocated by some for the treatment of operable as well as inoperable gastric carcinoma.

In 1903, John Blair Deaver of Philadelphia read a paper, "On Gastroenterostomy," in which he reviewed the historical aspects of the operation and described its widespread usage in treating obstructing pyloric carcinoma, duodenal and gastric ulcerations, gastroptosis, acute dilatation of the stomach, pylorospasm, tabes dorsalis, and various functional disorders. He made the important statement that a chronic ulcer in the vicinity of the pylorus might require a pylorectomy. Deaver made a plea for early operation in cases of gastric ulcer and believed if simple gastroenterostomy was done early, the subsequent development of gastric cancer could be avoided. He favored gastroenterostomy as a prophylactic operation as it was widely taught that many cases of gastric ulcer underwent malignant degeneration. He favored a short loop retrocolic gastrojejunostomy, and mentioned the prevention of circulus vitiosus by the addition of pyloric occlusion to gastrojejunostomy. In later years, Deaver largely abandoned gastroenterostomy and advised some type of gastric resection. Deaver was described by his colleagues as being rough, ready, and radical.

In 1906, Herman Tuholske of St. Louis described the unique and interesting experience of observing Professor Theodor Billroth of Vienna perform the first successful pylorectomy on Theresa Heller for pyloric carcinoma January 29, 1881. Tuholske gave the impression that distal gastric resection was done with misgivings, watched with disapproval, and was a bold surgical exercise without permanent beneficial results. He stated that gastroenterostomy performed for definite indications and using proper methods forms one of the most brilliant chapters in the advance of surgery. He advised gastroenterostomy for treatment of gastric ulcers even in the presence of hemorrhage without excision of the ulcer, and without looking for bleeding points. He violently opposed the resectional teachings of Ludwik Rydygier, the Prussian surgeon who had done the first successful gastric resection for a benign gastric ulcer in September 1881. Although gastric carcinoma and gastric ulcer had been defined near the turn of the century as representing separate disease entities, this fact was not fully appreciated by many leading surgeons of the time.

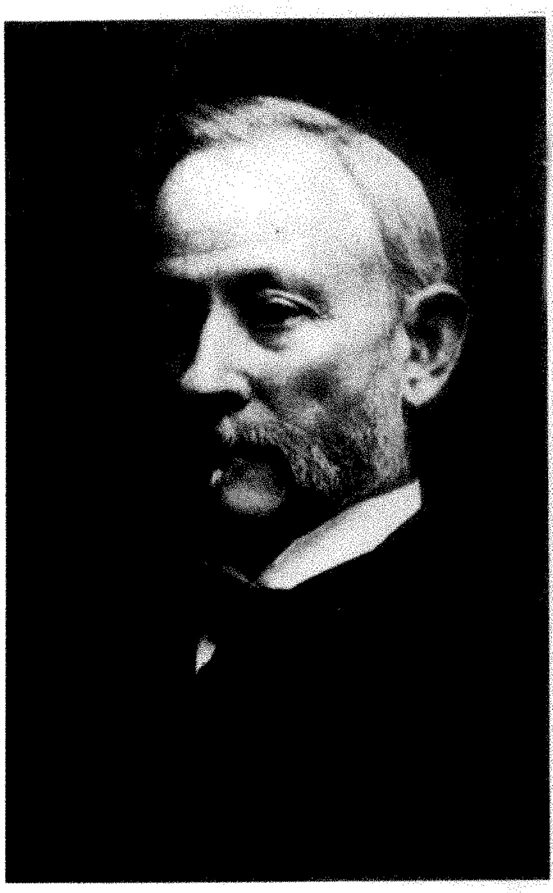
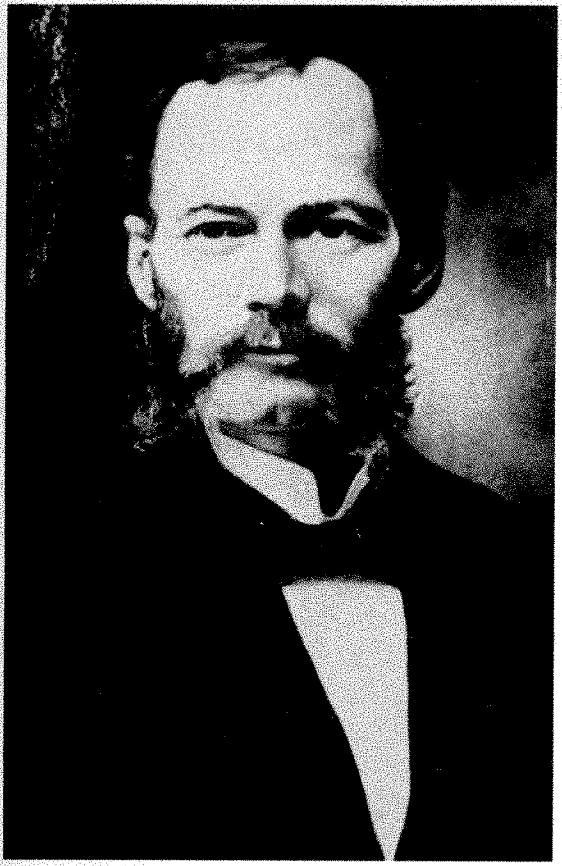


FIG. 1. William David Haggard, Sr., Nashville, Tennessee.

The first attempt at pylorectomy in America was by Randolph Winslow of Baltimore in 1884 (Fig. 3). Unfortunately the operation was unsuccessful. In 1921, Winslow became the 34th president of the association. Also, in 1884, Joseph Ransohoff of Cincinnati performed the first gastroenterostomy in America, the indication being a pyloric cancer, but the operation was not a success. Anton Wolfler had done a successful case in Billroth's clinic in September 1881. Ransohoff was elected to fellowship in the Southern Surgical and Gynecological Association in 1900. William L. Rodman of Philadelphia performed the first successful pylorectomy in this country and presented his case before the American Surgical Association in 1900 (Fig. 4). Rodman was likewise a member of the Southern Surgical and Gynecological Association and his son, Stewart later became a member.

In 1907, J. Garland Sherrill of Louisville was the first to describe before the association a distal gastric resection done for gastric ulcer, and the operation was successful. He was among the first to stress the importance of distinguishing between gastric ulcer, duodenal ulcer, and gastric carcinoma.

In the early 1900s, acute gastric dilatation following gastrojejunostomy was a frequent complication associated with high morbidity and mortality. It also was



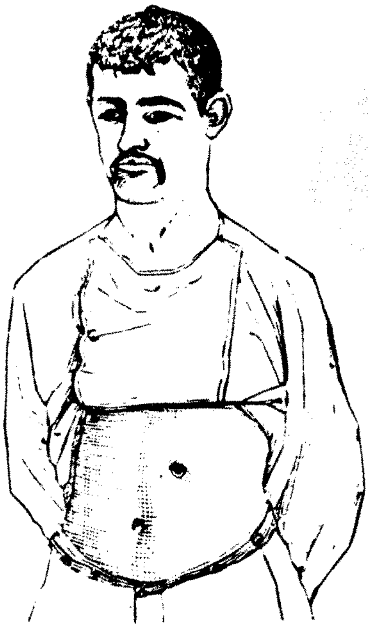


FIG. 2. William Boddie Rogers.

observed as a complication of other operations. Thomas C. Witherspoon of Butte, Montana and George A. Hendon of Louisville discussed the complication in depth, and were puzzled as to the cause and believed that all known methods of treatment generally gave unsatisfactory results.

James E. Thompson of Galveston (no relation to our JIM), presented a paper in 1912 on "Fatal Hemorrhage from Erosion of the Gastroduodenal Artery by Duodenal Ulcer." Thompson later became the 32nd president of the association. It was the general opinion of many surgeons that a gastroenteric shunt would arrest active hemorrhage as a result of diverting the gastric contents. Thompson was among the first to suggest either excising the bleeding ulcer or suturing the anterior and posterior walls of the duodenum at the site of the ulcer. Floyd McCrae of Atlanta, the 17th president, stated that he had witnessed one of the associates of Berkeley Moynihan of Leeds carry out such a maneuver. Moynihan was an honorary member of the association. Thompson mentioned two patients in whom he did not attempt to arrest hemorrhage while performing gastrojejunostomy and stated that he had allowed his two patients to slip through his fingers.

In 1912, Frank Martin of Baltimore described two successful cases of pylorectomy done for distal gastric ulcers. In one case an early carcinoma was found on microscopic study. Martin advocated gastroenterostomy for duodenal ulcer, but for ulcers located near the pylorus, a Rodman-type resection was used for fear of the existence of malignancy. He recalled that 20 years prior he had observed L. McLane Tiffany of Baltimore, the eighth president, perform a gastroenterostomy for a pyloric lesion, and later the patient died of widespread metastasis. Martin described his technique of performing pylorectomy in which he circumferentially stripped the serosa and muscularis from the pyloric area of the stomach. The mucosa and submucosal pyloric tube was then removed between crushing clamps and the duodenal and gastric ends closed with silk. A posterior gastroenterostomy was then accomplished.

In 1915, Dick Barr of Nashville likewise reported a successful pylorectomy and outlined his technique of suturing the mucosa and submucosa as a separate layer in performing the gastroenteric anastomosis.

John Young Brown of St. Louis, who became the 26th president, was the first to report before the association in 1914 the surgical closure of a perforated duodenal ulcer. Although surgical closure of a gastric ulcer had been attempted by Mikulicz in 1884, the first successful closure of a gastric ulcer was by Ludwig Heusner of Germany in 1892. The first successful closure of a perforated duodenal ulcer was by H. P. Dean of London in 1894. Brown used suture material to close the perforation with reinforcement by an omental graft and the patient survived. He did not perform a posterior gastroenterostomy as previously suggested by both Braun and Moynihan, but did carry out a feeding jejunostomy which was later closed. A posterior gastroenterostomy as definitive treatment for the duodenal ulcer was done at a later date. In discussion, Samuel A. Mixter of Boston reported three patients with perforation who were practically pulseless at the time of operation. Rather than attempt closure he placed a large tube in the perforation which was brought out through the abdominal wall. Fortunately all three patients survived and the fistulas closed spontaneously. Francis Reder of St. Louis discussed the calloused perforated ulcer that could not be surgically closed. He advised drainage of the area with packing, but unfortunately the patient died. A second patient survived after surgical closure. In further discussion, W. P. Carr of Washington, D.C. mentioned two patients with perforation whose tissues were such that he could not obtain a secure closure. He therefore performed a pylorectomy and both patients survived. One of the two was later found to have a distal gastric carcinoma. One patient was constructed with an end-to-end gastroduodenostomy and the other with a gastroenterostomy. These two patients represent the first cases presented before the association with acute perforation treated by primary resection. In 1902, C. B. Keetley of London performed the first primary resection for an acute perforation. Carr also mentioned a case of acute duodenal ulcer perforation that he treated with a gastroenterostomy along with placement of a gauze pack to the area of the perforation.

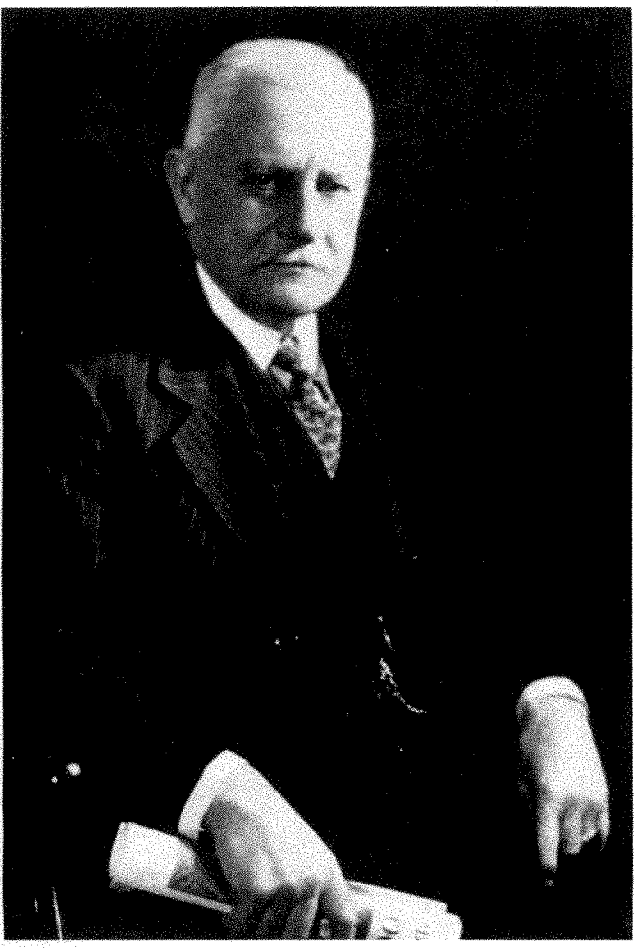


FIG. 3. Randolph Winslow.

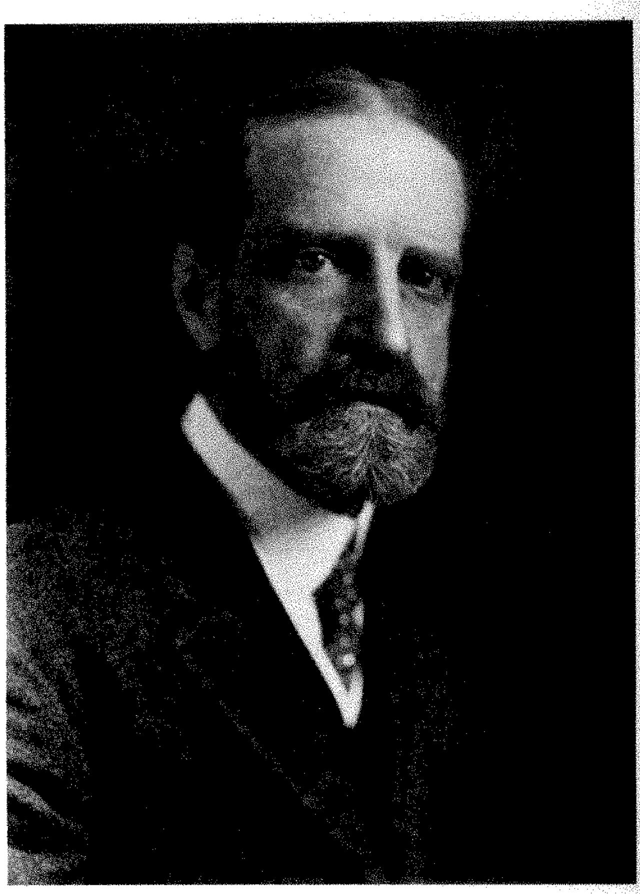


FIG. 4. William L. Rodman.

In 1915, Robert C. Bryan of Richmond described a single case of perforated ulcer involving the proximal jejunum in a patient who had undergone no previous abdominal surgery (Fig. 5). The perforation was located 3 inches distal to the duodenojejunal junction. Surgical closure was impossible; therefore, a piece of omentum was plugged into the opening and the wound was drained. The patient died the next day. The patient had a 2-year history of upper abdominal pain with a diagnosis of stomach ulcer. At the time of operation, Bryan

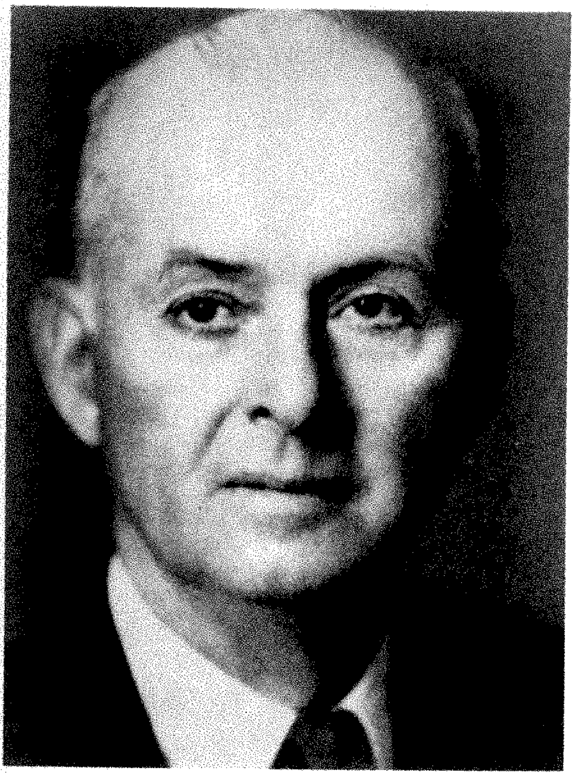


FIG. 5. Robert C. Bryan.

found the duodenum to be scarred and plastered against the posterior parietal peritoneum. The jejunum in the area of the perforation was noted to be white and was thickened. Bryan mentioned that Wagner had reported a perforated ulcer of the jejunum in 1861, 20 years before the first gastroenterostomy was performed. Several years later Edward Richardson of Boston was able to collect from the literature 10 cases of perforated jejunal ulcers without previous abdominal surgery and presented them before the association. Two of the cases had a pyloric and duodenal ulcer. No mention was made in either Bryan's or Richardson's paper of excessive gastric secretion, or the presence of a pancreatic tumor. Unfortunately, Bryan obtained no autopsy material when his patient died.

In 1916, through action by the council, the Southern Surgical and Gynecological Association became the Southern Surgical Association.

Charles N. Cowden of Nashville in 1919 discussed perforations of the gastrointestinal tract. He stated, "Never let the sun shine or set on this condition without an attempt at relief. Operations should be done as expediently as possible, doing only what is necessary, and artistic ideas should be left to less urgent cases." Cowden discussed the history, signs, and symptoms of an acute perforation. He stressed that the pain is usually sudden, sharp, and severe, but made the astute point that when perforation occurs with acute appendicitis, the abdominal pain lessens and the abdominal findings decrease, but the key to diagnosis is the increasing rapidity of the pulse rate. Cowden deplored treating a perforated duodenal ulcer with drainage alone. He emphasized the importance of surgical closure along with reinforcement by omentum or an adjacent loop of bowel. He further stated that in every case of perforation, irrespective of the condition of the patient, there was an absolute indication for immediate operation. When symptoms point rather definitely to perforation but the diagnosis is somewhat in doubt, exploration is safer than delay. He emphasized that shock was no contraindication to exploration.

In 1916, Robert C. Coffey of Portland, Oregon discussed chronic gastric and duodenal ulcers. He believed that 50% of such ulcers should be treated surgically, and posterior gastroenterostomy was his operation of choice. He stated that he had become somewhat annoyed that the procedure was being performed by country general practitioners and general surgeons who had no special training in doing such cases. He emphasized the low mortality with gastroenterostomy performed by members of the Mayo Clinic, the Roosevelt Hospital Staff in New York, and his own private service. Coffey's mortality rate was in the range of 5% among 150 patients. For those ulcers near the pylorus he performed ulcer excision with a Finney pyloroplasty. For gastric ulcers along the lesser curvature he preferred a Balfour cautery destruction plus either pyloroplasty or gastroenterostomy. For large stomach ulcers either a pyloroplasty or gastroenterostomy was done followed by treatment with a medical regimen. If this method failed, some type of gastric resection was then done. Coffey strongly believed that with ulcers in the pyloric area one should be suspicious of carcinoma, and a pylorectomy should be performed. In discussion, J. M. T. Finney, Sr., of Baltimore, the 25th president, described his wide experience with pyloroplasty (Fig. 6). At the 1902 meeting of the American Surgical Association Finney first outlined the technique of his operation. At the time, Arthur Dean Bevin of Chicago told Finney that the operation was too difficult technically and that Finney was straining at a gnat and trying to swallow a camel.

A few years later at the Southern Surgical Association, Charles H. Mayo of Rochester, Minnesota mentioned a large series of both gastric and duodenal ulcers and stated that gastroenterostomy was the treatment of choice at the Mayo Clinic irrespective of the location of the ulcer. However, if there was suspicion of cancer present in the margin of a gastric ulcer, the Mayo Clinic surgeons combined cautery destruction with gastroenterostomy. In a lively discussion Finney stated, "Gastroenterostomy, like an amputation is always the confession of defeat. Gastroenterostomy is never an operation of choice but always an operation of necessity." (With Dr. Finney, Sr.'s great interest in pyloroplasty, it is noteworthy that many years later his son, George, the 72nd president, read a paper on his experiences with duodenal ulcer surgery and did not mention pyloroplasty.)

At this same meeting, Edward P. Richardson of Boston presented a paper on acute and subacute perforations of the stomach and duodenum from the Massachusetts General Hospital. He mentioned that in the years from 1896 to 1900 there was a 75% mortality rate among patients with a perforated gastric ulcer and a 100% mortality rate among the duodenal ulcer perforations. In contrast, from 1911 to 1915 there was a 57% mortality rate among the gastric ulcer group and only a 20.8% mortality rate among duodenal ulcer perforations. He stated that advanced age was an important factor in mortality and that the degree of intra-abdominal spillage was greater in gastric ulcer patients. Packing and drainage without suture as used in the earlier cases contributed greatly to mortality.

Stuart McGuire of Richmond, the 22nd president and son of Hunter Holmes McGuire, the second president, gave a delightful and comprehensive review of duodenal fistula in 1919. He mentioned that such fistulas may follow a right nephrectomy, biliary and gastric operations, and inadvertent injury to the duodenum. He mentioned the excessive fluid loss, skin excoriation, weight loss, and malnutrition that occur as complications. He believed that with duodenal injury occurring during a right nephrectomy the fistula could usually be closed as it was located on the posterior duodenal wall. However, with a duodenal fistula following biliary or gastric surgery, the fistulous opening was usually on the anterior wall, and if such a fistula developed after surgery it did not render itself to direct suture. He suggested that in certain cases of persistent fistula, posterior gastroenterostomy and pyloric occlusion as advocated by Deaver was a reasonable method of treatment. McGuire mentioned a single case in which a fistula developed after biliary tract surgery and there were such extensive adhesions in the upper abdomen that he could not perform gastroenterostomy and an exclusion procedure. He treated the patient with a feeding jejunostomy and recovery eventually took place.

Throughout the 1920s and into the late 1930s, simple gastroenterostomy remained the preferred treatment of duodenal ulcer by many American surgeons. However, for treatment of gastric ulcers, many surgeons began to advocate some type of resection with ulcer excision for fear of the existence of malignancy or for fear of a benign ulcer undergoing malignant transformation.

In 1920, J. Shelton Horsley of Richmond presented the first paper before the association on marginal ulcer following gastroenterostomy. Both Horsley and Donald Balfour of Minnesota observed that gastroenterostomy was more frequently followed by marginal ulceration if the patient had a patent pylorus and an open duodenal outflow tract. Gastrojejunostomy gave better results if there was a cicatrical obstruction at the pyloric canal, as pyloric stenosis prevented the lowering of alkalinity of the duodenal contents and the gastroenteric stoma was more adequately bathed with biliary and pancreatic contents. Horsley reasoned that, instead of magnifying the importance of technical errors of the operation in promoting recurrent ulcers, one should justly regard the violation of broad physiologic principles as the cause of jejunal ulcer. Horsley expressed dissatisfaction with the results of gastrojejunostomy for both gastric and duodenal ulcer, and cited the work of Frank Smythe of the Augustana Hospital in Chicago. Smythe observed that among 273 patients with a gastroenterostomy only 20.9% were symptom free. In treatment of a marginal ulcer after gastroenterostomy, Horsley advised takedown of the gastroenterostomy, closure of the jejunum, closure of the stomach, and the addition of a pyloroplasty. He further stated that it seemed logical to conclude that if a pyloroplasty is the proper treatment for the cure of a jejunal ulcer after gastroenterostomy, then

FIG. 6. J. M. T. Finney.

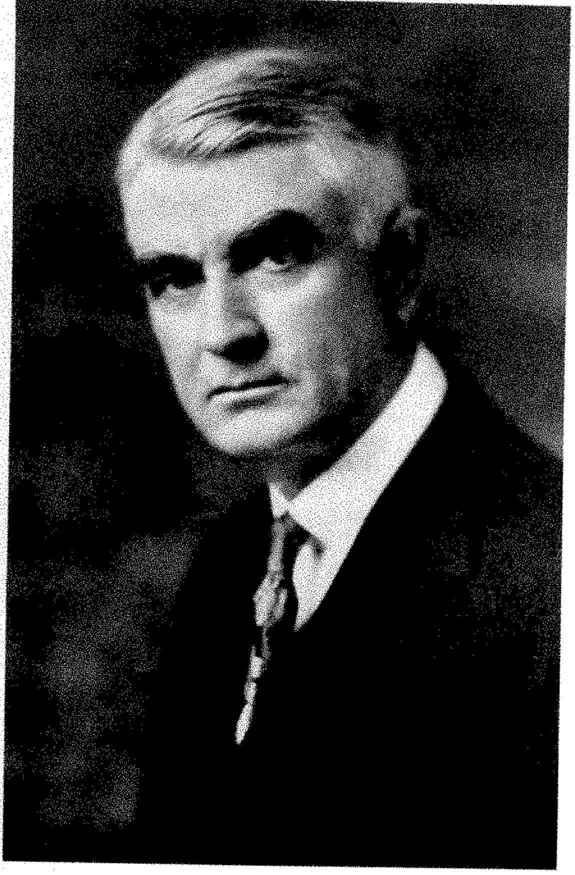


FIG. 7. William J. Mayo.

pyloroplasty in the first place should have been excellent prophylactic treatment for jejunal ulcer. He expressed his recent interest in pyloroplasty in which he excised a longitudinal ellipse of the anterior pyloroduodenal canal and closed it in a transverse fashion. Twenty-four of these procedures were reported, most being done for primary ulcer disease. Horsley further mentioned that a long interval may elapse before the development of a marginal ulcer. He stated, "It is only after continual perversion of the physiology of the jejunum that nature begins to protest." Will Mayo of Rochester in discussion believed that most recurrent ulcers after gastrojejunostomy were due to a combination of faulty operative technique and the use of nonabsorbable suture material. (Fig. 7) However, in his own experience only 1.2% of patients had a recurrence after gastroenterostomy.

That same year, Charles H. Mayo of Rochester presented a paper on gastric and duodenal ulcer and stated that gastroenterostomy was still the treatment of choice at the Mayo Clinic, irrespective of the location of the ulcer. In an analysis of 647 operations for ulcer of the stomach, the average mortality rate after gastroenterostomy was 3.2%, which was more than double the average mortality rate in 2734 operations performed during the same period for duodenal ulcer.

At the 1921 meeting, George Crile, Sr. of the Cleveland Clinic was beginning to show an interest in gastric resection for both gastric and duodenal ulcer. However, he still largely favored simple gastroenterostomy and advised resection as a secondary operation if gastroenterostomy failed. He also was beginning to show an interest in pyloroplasty over gastrojejunostomy.

During the next few years Crile's enthusiasm for gastric resection over pyloroplasty increased. He presented an interesting analogy between hyperthyroidism and peptic ulcer. Crile stated that hypersecretion of acid was a central figure if not the cause of peptic ulcer and that hypersecretion of thyroid hormone was the central feature if not the actual cause of hyperthyroidism. Both conditions flourish in an atmosphere of stress and striving. Both are induced and augmented by overwork and both are improved by a holiday with complete change in environment. Crile further added that both diseases are present among those individuals of keen desires and internal struggles who are carrying the burdens of civilization. Hyperthyroidism may be reduced to normal thyroidism by excision of a sufficient amount of the secreting gland, and hyperacidity is reduced by excision of a sufficient portion of the acid secreting area of the stomach. He further stated that arterial ligation gave temporary relief of hyperthyroidism as gastroenterostomy sometimes gave only temporary relief from ulcer disease. He remarked that hyperthyroidism had been all but conquered, but the hypersecretion of gastric juice and chronic ulcer had all but defeated the surgeon and the physician. He stated that pyloroplasty in treatment of an ulcer of the lesser gastric curvature would seem analogous to excision of the thymus gland for hyperthyroidism. Thus, he believed that in our surgical thinking we should now start anew, and in the treatment of ulcer disease use gastric resection as practiced by Finisterer, Haberer, and other continental surgeons. He recalled that their mortality rate had been reduced to 2–3% and their results were wholly different from the results of gastroenterostomy and cautery destruction of ulcers. Thus, he believed that the philosophy of the surgical treatment of ulcer should change from local excision or gastric drainage to the control of gastric hypersecretion by resection of a portion of the stomach. Thus, Crile was one of the first surgeons in America to strongly advocate this change in surgical therapy.

A lively discussion followed this 1923 presentation. Both Shelton Horsley of Richmond and William D. Haggard, Jr. of Nashville made pleas for simpler operations. Richard A. Barr of Nashville mentioned that extensive operations done for ulcer by the continental surgeons not only cured the small ulcer but also served to prevent future formation of ulcer. Charles H. Mayo of Rochester said, "I believe few surgeons today would permit the primary resection of a large part of a normal stomach on themselves for the relief of a small duodenal ulcer" (Fig. 8). Donald Balfour of Minnesota remarked that some sort of partial gastrectomy should be done for large ulcers in the distal portion of the stomach, but that for ulcers in the proximal stomach, excision or cautery destruction combined with gastroenterostomy was his method of choice. R. C. Coffey of Portland, Oregon stated that he had obtained good results using pylorectomy after the method of Rodman for distal stomach ulcers. From the overall discussion one gained the impression that members of the Southern Surgical Association were slowly but cautiously beginning to give some thought to the more radical surgical approach to the ulcer problem.

Charles H. Mayo and his son-in-law, Fred W. Rankin of the Mayo Clinic, the latter to become the 50th president, presented the first paper before the association on gastrojejunocolic fistula after gastroenterostomy. They believed that the incidence of this complication varied between 1 and 3%, and they also stated that such cases should not be treated by a massive operation but that the fistula should be taken down, the stomach and colon openings closed, and either a new gastrojejunostomy or a pyloroplasty constructed.

The 1923 meeting contained several more interesting papers on gastroduodenal ulcer disease. J. M. T. Finney, Sr. of Baltimore presented a new method of gastroduodenostomy (end-to-side) along with illustrations. He did the reconstruction following a pylorectomy. In a recent review of the literature he found that Hans Haberer of Germany had described a similar technique. The procedure was applicable for both distally located gastric ulcer and duodenal ulcer. In performing the anastomosis, the cut end of the duodenum was closed and the anastomosis was made between the open cut end of the stomach and the side of the second portion of the duodenum just distal to the duodenal stump closure.

Charles H. Mayo of Rochester also presented his method of gastroduodenostomy following a limited distal resection using a large flap gastroduodenostomy instead of a narrow one as proposed by Finney.

At the same meeting, Donald C. Balfour of Rochester, Minnesota presented a paper entitled "Partial Gastrectomy for Gastrojejunal Ulcer." This represented the first presentation at the Southern Surgical Association advising resection for this complication. Methods previously cited had been operations of lesser extent. Balfour believed that gastrojejunal ulcer following gastroenterostomy took place in about 2% of cases, and that the condition could be treated by one of three methods. Excision of the recurrent ulcer could be done when it was small, and at the same time, the gastroenterostomy could be enlarged. As an alternate, one could take down the gastrojejunostomy, excise the recurrent ulcer, and close the openings in the stomach and jejunum and perform a pyloroplasty. Also, another method was to remove the gastrojejunostomy, excise the recurrent ulcer, and close the opening in the jejunum. This was followed by resection of the pyloric end of the stomach including the old opening of the anastomosis. Restoration of continuity could be done by one of several methods. The latter operation was termed a "partial gastrectomy," and it possessed several advantages. This rather radical approach to the treatment of marginal ulcer was certainly a deviation from the method of treating a primary ulcer by gastrojejunostomy alone or by cautery destruction with gastrojejunostomy. Eleven years later in 1934, Balfour presented another paper on jejunal ulcer and strongly favored gastric resection.

FIG. 8. Charles H. Mayo.

At the 1924 meeting, Frank K. Boland of Atlanta, later the 47th president, presented his experience with simple closure of acute perforated duodenal ulcer

FIG. 9. William Haggard, Jr.

among seven patients. He stressed the difficulty at times in making the correct diagnosis and mentioned that ulcer perforation could be confused with acute appendicitis. His treatment of choice was immediate laparotomy with closure of the perforation using a pursestring suture. If the ulcer was amendable to excision this was carried out at the same time. He drained the right upper quadrant as well as the pelvis, but did not perform a concomitant gastrojejunostomy. In discussion, Harley Shands of Jackson, Mississippi remarked that he added a gastrojejunostomy to simple closure only if closure appeared to compromise the duodenal opening. Shelton Horsley of Richmond remarked that he added a pyloroplasty in some cases, and if he used a gastrojejunostomy he would always put a ligature around the pylorus. He believed that the ligature placed the duodenum at rest and promoted healing. Dick Barr of Nashville gave a delightful discussion, as he always did at the Southern Surgical Association, and he would frequently challenge the Mayo brothers concerning their results with simple gastrojejunostomy. Barr stated that he had had poor results with gastrojejunostomy for treatment of a nonperforated ulcer, and therefore, he could see no advantage to adding a drainage operation to closure of a perforated duodenal ulcer.

In 1926, W. D. Haggard, Jr. of Nashville, the 30th president, discussed "Resection of the Stomach and Duodenum for Ulcer" (Fig. 9). Haggard mentioned that ulcer surgery was now going through an interesting period, and that the best method of surgical cure was open to question. He mentioned that the conservative attitude of American surgeons was being attacked, and recalled that on a recent visit to the surgical clinics of Europe he had observed radical operations being done on the stomach for ulcer disease. He believed that pyloroplasty as currently advocated by some American surgeons was not an ideal operation, but stated that he was not ready to give up on gastroenterostomy entirely. He was, however, beginning to give serious consideration to performing distal gastric resection with a Billroth I reconstruction for distally located gastric ulcers. A larger resection was advocated with a Polya-Balfour anastomosis for more proximally located gastric ulcers. Haggard stressed that 15% of gastric ulcers had been shown to be microscopically malignant, and he believed that many benign gastric ulcers underwent malignant changes. He also stated that the percentage of gastric ulcers currently being dealt with by resection at the Mayo Clinic was now up to 16.4%. He also mentioned sleeve or segmental resection of the stomach for midbody lesions with a cure being obtained in as high as 95.2% of cases. Haggard also advised excision of all bleeding ulcers of the duodenum and believed that as his experience increased he would come to resect more and more duodenal ulcers. He mentioned that George Crile, Sr. of Cleveland, John B. Deaver of Philadelphia, and A. A. Berg of New York were beginning to favor gastric resection.

In discussion of Haggard's paper, J. A. Crisler of Memphis, a strong advocate of gastrojejunostomy, stated, "I hope that dear splendid Dr. Haggard will not use his oratorical prowess to such an extent as to condemn this very useful and necessary operation. He has that splendid way about him of being able to make one believe that black is white and vice versa. It is hoped that he will spare those of us who have had many reasons to become endeared to this particular surgical procedure the privilege of continuing the same without his erstwhile condemnation."

In 1926, E. Starr Judd and Gunther W. Nagel of Rochester, Minnesota read a paper entitled "Duodenitis." They had encountered patients with ulcer-like pain, but who had no demonstrable duodenal ulcer crater or deformity. In those patients refractory to medical management, the authors advised an operation consisting of opening the first portion of the duodenum and distal stomach with excision of the diseased mucosa. The anterior portion of the pyloric sphincter was cut and the anterior gastric and duodenal walls were then sutured together. If the inflammatory process was too extensive, a gastroenterostomy was the treatment of choice. At the Mayo Clinic, 94% of such patients obtained an excellent result.

During the late 1920s and into the late 1930s, discussions on ulcer disease continued with many members still favoring gastroenterostomy or pyloroplasty for chronic duodenal ulcer. Some type of resection with ulcer excision or cautery destruction was being increasingly advocated for gastric ulcer. Gastric resection was also being increasingly advocated as the operation of choice to correct jejunal ulcer and lesser operations as excision, closure of the stomach, and closure of the jejunum were being abandoned. A few interesting comments from papers presented during the late 1920s and 1930s are listed below.

J. Tate Mason of Seattle reported a 4.5% mortality rate with gastrojejunostomy among 90 patients. The results were unsatisfactory in only 12.8%. Robert C. Coffey of Portland, Oregon stated that there was no operation in abdominal surgery that gave more satisfactory results than gastroenterostomy. John B. Deaver of Philadelphia still believed that conservative operations were the treatment of choice, but that he occasionally did a pylorectomy for an ulcer in a mobile duodenum or when the ulcer was located in the pyloric area. D. F. Jones of Boston read a letter before the association from a surgical friend who had recently reported 221 subtotal gastrectomies for duodenal ulcer with 95% good results. The friend stated that there was no satisfaction or convenience from gastroenterostomy or from other types of pyloroplasty. The friend also mentioned 25,000 gastrectomies reported in a survey from Vienna, which encompassed a collected series of operations throughout various European countries. The incidence of marginal ulcer was less than 0.5%, but recurrences were 20–25% among those patients who received gastroenterostomy alone. The friend also told Jones that subtotal gastric resection for duodenal ulcer had been the most satisfactory operation in the upper abdomen performed in his institution. (It was believed that this letter was composed by A. A. Berg of the Mt. Sinai Hospital in New York.) Donald Balfour of Rochester, Minnesota disagreed with the letter and believed that there would be too many deaths from such a radical operation. Urban Maes of New Orleans stated that gastroenterostomy still gave excellent results for duodenal ulcer and slightly less good results for gastric ulcer. Frederic W. Bancroft of New York described his operation of pyloric exclusion and distal resection for duodenal ulcer. This was a modification of the Devine operation, and was suggested to Bancroft by Lewis Gregory Cole. It had the advantage of coring out the antral mucosa, and Bancroft believed that it had merit over the standard gastric resection. Frank Lahey of Boston expressed dissatisfaction with gastroenterostomy, and mentioned that the incidence of stomal ulcer was 16–24%. Lahey was now giving more and more attention to gastric resection for the treatment of ulcer disease.

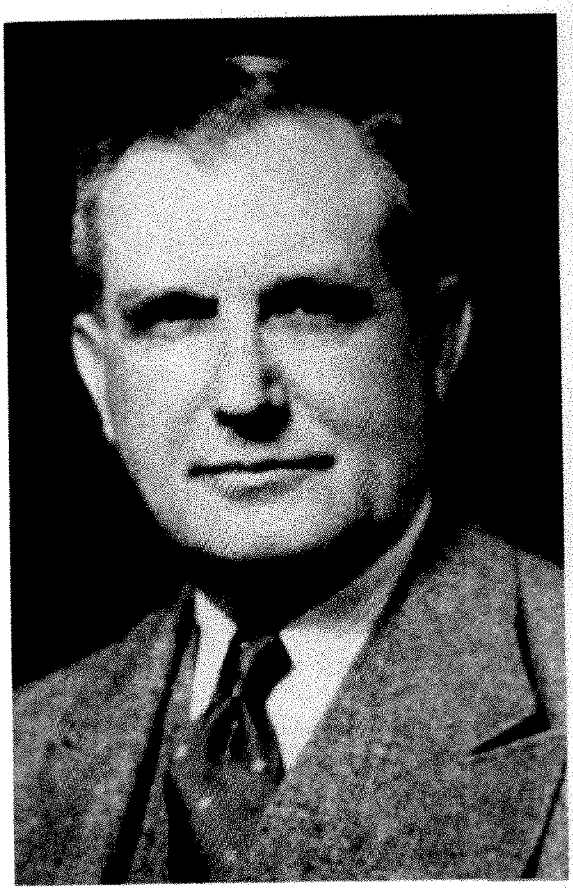


FIG. 10. Roy D. McClure.

A major breakthrough occurred at the 1939 meeting when Roy D. McClure of Detroit advocated partial gastric resection for both gastric and duodenal ulcer (Fig. 10). The Henry Ford Hospital group had reduced the mortality rate to 5%, and in their last 53 cases there had been but one death. McClure was careful to state, however, that the procedure should not be undertaken by the occasional operator. In discussion, Samuel D. Marshall, who had been trained by Roy McClure and who was now at the Lahey Clinic, heartily endorsed high gastric resection for both gastric and duodenal ulcer. He mentioned that 88 consecutive resections had been done at the Lahey Clinic with only one death. Marshall favored an antecolic anastomosis, whereas McClure favored the retrocolic technique.

In 1941, young Waltman Walters of the Mayo Clinic, the son-in-law of Will Mayo, caused an upraising of eyebrows at the Southern Surgical Association when he stated that benign gastric ulcer was now being treated at the clinic by subtotal gastrectomy with a mortality rate of 2.2%. Fewer gastroenterostomies were being done for duodenal ulcer, and local excision or cautery destruction of gastric ulcer combined with gastroenterostomy was being used only in poor-risk patients.

At the same meeting, Arthur W. Allen of Boston and his young guest Claude Welch also endorsed gastric resection and mentioned that it had taken them some years to realize that lesser procedures were associated with a high percentage of failures. They also discussed the Devine and Finisterer exclusion operations and the reasons for their failures. William Francis Reinhoff, Jr. of Baltimore cited 260 consecutive elective operations for duodenal ulcer using subtotal gastrectomy with a failure rate of only 8%.

In 1944, Samuel D. Marshall of the Lahey Clinic stressed the high mortality in performing a one-stage *en bloc* resection for gastrojejunocolic fistula. The mortality rate was 63% among eight patients. He therefore advocated a two-stage procedure and reported a mortality rate of 7.1%. Twelve years later with improvements in anesthesia, surgical techniques, and antibiotic usage, he favored the one-stage *en bloc* operation and reported a respectable mortality rate of 6%.

In 1946, Waltman Walters of Rochester, Minnesota presented the first paper on vagotomy before the association. The presentation was entitled, "Gastric Neurectomy for Gastric and Duodenal Ulceration." Three years earlier, Lester Dragstedt of Chicago had repopularized vagotomy, and preliminary reports had appeared in America by Francis Moore of Boston and Keith Grimson of Durham, North Carolina. Walters mentioned 66 patients and was impressed with the gastric motility disturbances, diarrhea, and emptying problems that occurred. He did not endorse vagotomy as the primary operation for duodenal ulcer, but believed that it might be indicated for the treatment of a recurrent ulcer after adequate gastric resection. He mentioned a 12.5% early recurrence rate with an additional 16% of patients complaining of significant postoperative problems. In subsequent reports and discussions before the association, Walters showed very little enthusiasm for vagotomy with drainage except in selected circumstances. He actually stated that vagotomy with gastroenterostomy probably had no advantage over gastroenterostomy alone. Frank Lahey of Boston advised caution with the procedure and likewise compared it with gastroenterostomy.

On the other hand, Keith Grimson of Duke, in his presentations and discussions during the 1940s and early 1950s, expressed enthusiasm for vagotomy and gastroenterostomy, and over the years reported 335 patients with 91.4% obtaining satisfactory results. At times rather heated discussions occurred at the Southern Surgical Association between the advocates of high subtotal gastrectomy and those who favored vagotomy with drainage for duodenal ulcer. At one of the national meetings one renowned surgeon went so far as to state that perhaps a moratorium should be declared concerning vagotomy. It was the consensus of opinion among most surgeons that vagotomy and drainage should not be used in the treatment of gastric ulcer and that subtotal gastrectomy with removal of the ulcer was the treatment of choice.

Michael E. DeBakey and the group in Houston were largely responsible for popularizing definitive operation in America for selected cases of acute duodenal ulcer perforation, a method that had been used on the European continent since the first part of this century. Beginning in 1952, the Houston group showed in several papers that subtotal gastrectomy and later vagotomy/antrectomy in selected cases could be performed with a very low mortality and with excellent long-term results. DeBakey later mentioned 535 primary resections with a mortality rate of only 2.2%.

John M. Emmett of Clifton Forge, Virginia gave two separate discussions on gastric resection for acute duodenal ulcer perforation. He cited 76 patients with no mortality and a 5% recurrence rate. The patients were selected but he was performing a primary resection in 91% of his cases.

It is of interest that in 1955, Benjamin F. Byrd of Nashville reported 191 patients with a perforated duodenal ulcer treated by simple closure at the Vanderbilt University Hospital over a 25-year period with an acceptable mortality rate of only 7%. At the time of the study only one definitive operation had been done at Vanderbilt for a perforated duodenal ulcer. Henry Cave of the Roosevelt Hospital in New York also advocated primary resection in selected cases of acute duodenal ulcer perforation.

During the 1950s there was a gradual but increasing interest in vagotomy for duodenal ulcer due to the tireless efforts of Lester Dragstedt of Chicago (Fig. 11). Dragstedt weathered rather severe criticism in the early years from many of his colleagues regarding vagotomy.

In 1952, Leonard W. Edwards of Nashville presented the first paper before the association on truncal vagotomy with antrectomy for treatment of duodenal ulcer (Fig. 12). Thirty-four cases were described with a follow-up extending to 6 years. Edwards had performed the first such operation in January 1947, unaware that Reginald Smithwick of Boston had performed a similar operation in October 1946. Smithwick presented his paper before the American Surgical Association in 1951. In discussion of Edwards' paper, Frank Lahey stated, "In the past few years vagotomy has been frequently discussed often with too much pride and equally too much prejudice, and one can make bad friends depending on which side you happen to place yourself regarding vagotomy." Lahey favored resection but warned about the complications that can occur when the duodenum is severely diseased.

During the next two decades, H. William Scott, Jr. with the Vanderbilt/St. Thomas surgical groups presented several additional papers on vagotomy/antrectomy, and in a substantial number of cases reported an ulcer recurrence of less than 1%, and an elective mortality rate of 1.5% (Fig. 13). They stressed the combined operation was suitable for all complications of duodenal ulcer, and it could be done with safety except in high-risk patients and in those with an intense inflammatory process about the duodenum.

Much discussion was given to this operation throughout the late 1950s, 1960s, and early 1970s, and the procedure was highly endorsed by such members as Robert Coffey of Washington, D.C., the 81st president, George Crile, Jr. of Cleveland, Walter Burdette of Salt Lake City, George Jordan of Houston, Joe Hamilton of Louisville, Julian Quattlebaum, Sr. of Savannah, and others. One dissenting remark that stands out was made by Mark Ravitch, at the time I believe from Chicago. He had the audacity to term the operation, "A ritual circumcision of the pylorus." Most surgeons came to acknowledge that vagotomy/antrectomy was the best operation to prevent recurrent ulcer. However, it was believed that vagotomy with drainage was a safer operation in inexperienced hands, among high-risk patients, and when an intense inflammatory process existed in the duodenum. Both procedures were now being widely used throughout the world, and case selection was stressed in choosing between the two operations. During this period one could see a gradual trend away from high subtotal resection for duodenal ulcer and a slow gradual acceptance of the two more conservative procedures.

In 1952, Isidore Ravdin of Philadelphia in discussing gastric ulcer and gastric carcinoma made a plea for immediate operation in every patient with a gastric ulcer for fear of missing the diagnosis of cancer. Samuel Marshall of Boston advocated an early but not an immediate operation, whereas Frank Lahey stated that he would like to operate on every patient with a gastric ulcer but he could not get the cooperation of his gastroenterologists. You may remember that the distinguished Sarah Jordan was at the gastroenterology helm at the time.

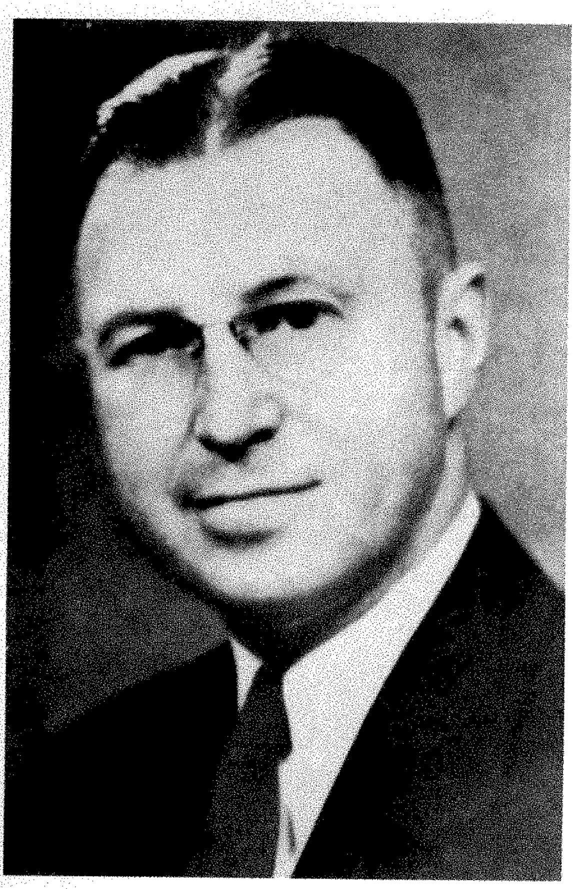
In the 1950s, massive upper gastrointestinal hemorrhage of undetermined origin constituted even a greater challenge than it does today as routine endoscopy was not available. Howard Gray of the Mayo Clinic believed that when the point of bleeding was undetermined, it was best to proceed with a high-blind subtotal gastric resection. James A. Kirtley, later the 77th president, and Douglas Riddell of Nashville advocated a generous gastrostomy as originally described by Frank Spencer, then of Baltimore, in order to search for the bleeding source.

FIG. 11. Lester Dragstedt.

About this time a more aggressive surgical approach was advocated for the treatment of the massively bleeding peptic ulcer. The problem was discussed in depth by George Mixter and William Hinton of the Bellevue Hospital in New York. Hinton described a most interesting patient who bled massively after a subtotal gastrectomy done for a bleeding duodenal ulcer. Over a 10-day period 118 units of blood were given. A transthoracic vagotomy was then carried out with prompt arrest of bleeding.

At the 1957 meeting, Isidore Cohn, Jr. of Louisiana State University, later the 97th president, made a significant contribution when he discussed giant gastric ulcers. He showed that only 8.6% of such ulcers at the Charity Hospital were malignant, whereas it had been taught that up to 80% of giant ulcers contained carcinoma. In a collected series of 613 giant gastric ulcers, Cohn found 71% to be benign. Waltman Walters in discussion believed that the larger the ulcer, the more prone it was to be a cancer.

William O. Barnett of Jackson, Mississippi in 1963 showed the value of a Roux-en-Y limb when faced with a difficult duodenal stump closure following gastric resection. Discussants reminded Barnett that when a severe inflammatory process was found in the duodenum



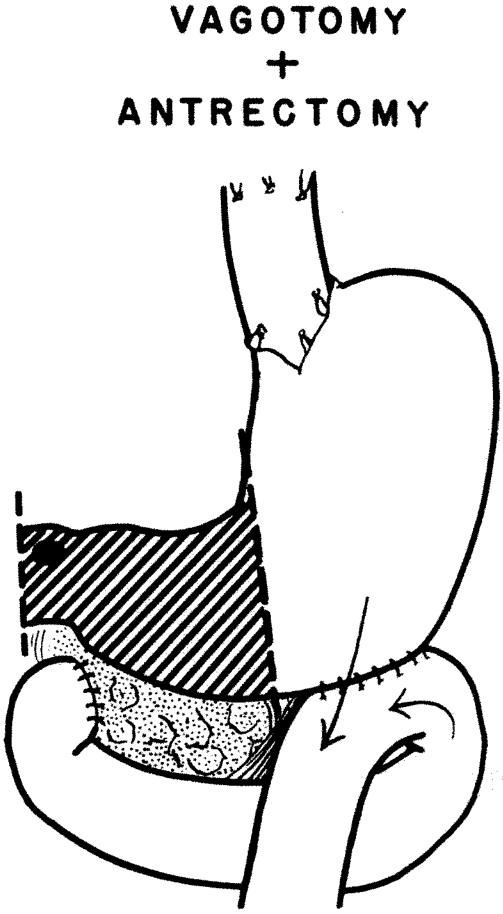


FIG. 12. Leonard Wright Edwards.

one should resort to a lesser procedure and not commit themselves to a gastric resection. Barnett responded by saying that severe pathology in the duodenum could not always be appreciated until one had divided the stomach and committed oneself.

During the 1960s four papers were presented on gastric freezing for the treatment of both duodenal and gastric ulcer by William Scott of Nashville, the 90th president, Raleigh White of Temple, Texas, Curtis Artz of Jackson, Mississippi, and William Shingleton of Duke. Each author cited early good results but mentioned the significant complications and later failures that followed this method. Never again was gastric freezing a topic for discussion at the Southern Surgical Association.

Claude Welch of the Massachusetts General Hospital in 1966 presented a paper on anastomotic ulceration. Welch believed that the ideal operation to prevent recurrence was vagotomy and a partial resection, and that when marginal ulceration followed a lesser procedure such as vagotomy and drainage, revagotomy and resection was the procedure of choice.

The surgical management of massive bleeding from peptic ulcer and bleeding from superficial gastric erosions were frequent topics of discussion during the 1960s. However, the first paper on postoperative gastric hemorrhage after operation on organs other than the stomach was presented by Kennedy Gilchrist of Chicago in 1957. This presentation aroused much interest among the members.

J. Englebert Dunphy of Portland, Oregon in 1964 described 239 patients with massive bleeding from duodenal ulcer. He believed that the best results were obtained with vagotomy and pyloroplasty and ligation of the bleeding vessel. There were others who advocated radical gastric resection or vagotomy with antrectomy.

In a 1968 paper, James Kirtley of Nashville discussed the management of superficial gastric ulcerations and believed that the best results were obtained with vagotomy and pyloroplasty and undersewing of the bleeding points. William Scott of Nashville made a pertinent statement when he said that he did not know what was the proper operation for such bleeding and that cases must be carefully individualized.

In 1971, Isidore Cohn and Carter Nance of New Orleans studied 768 patients with upper gastrointestinal bleeding who underwent operation at the Charity Hospital over a 5-year period. The overall mortality rate was 29% and was 44% for patients over age 60 years. The operative mortality rate for emergency operation was 31%. The authors believed that they had not been aggressive enough in advising early operations on massively bleeding patients. Several discussants emphasized the hazards of delayed operation, but there was no agreement among the discussants as to the best operative procedure to control hemorrhage.

A few highlights of papers presented between 1970 and 1980 included the experience of Theodor Drapanas of Tulane University at New Orleans, who discussed the surgical management of acute gastric mucosal hemorrhage. Drapanas studied 31 patients with near exsanguinating bleeding from superficial gastric erosions. He observed that among 19 patients treated by vagotomy and resection, there was no incidence of recurrent hemorrhage. However, among 10 patients who underwent a subtotal gastric resection without vagotomy, several rebled. The incidence of rebleeding in those patients who did not receive vagotomy was 50%. His experimental work showed that vagotomy produced a salutary effect in controlling mucosal bleeding by the opening of arterial venous shunts in the submucosa and by depleting vasoactive amines from the mast cells in the mucosa. Bradley Aust of San Antonio used extensive devascularization of the stomach to arrest gastric mucosal hemorrhage.

The management of postoperative alkaline reflux gastritis following operations on the stomach and duodenum was beginning to attract attention during the 1970s. William McCune of Washington, D.C. presented a most interesting paper concerning 11 patients with severe reflux that followed either vagotomy with drainage or vagotomy with resection. The importance of endoscopy with biopsy was emphasized in making the diagnosis. Each of the 11 patients was treated with a Roux-en-Y reconstruction and a hemigastrectomy. If the previous operation had been only vagotomy and pyloroplasty, a hemigastrectomy was added and very satisfactory results were obtained.

In 1973, Theodore Drapanas of New Orleans in discussing postoperative alkaline reflux gastritis cited 24 patients who were markedly benefited with a Roux-en-Y diversion or a Tanner-19 loop. A decade later Wallace Ritchie of Temple University in Philadelphia gave a scholarly presentation on the subject and attempted to outline objective preoperative data that was important in selecting candidates for operation.

During the 1970s adequate subtotal gastric resection for treatment of duodenal ulcer was no longer a topic of discussion at the Southern Surgical Association. Many surgical giants now believed that this operation would soon be of historical interest only for treatment of such ulcers.

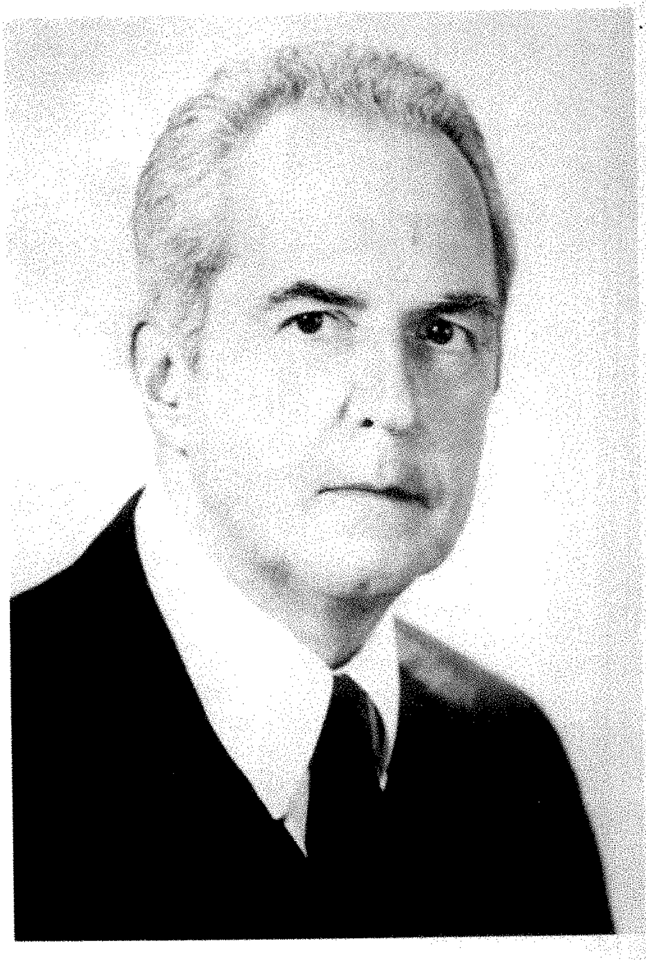


FIG. 13. H. William Scott, Jr.

In 1973, George Hallenbeck of Birmingham was the first to discuss proximal gastric vagotomy. His was principally an experimental paper, and Hallenbeck showed that histamine and pepsin-induced secretion of hydrochloric acid were reduced with the operation and he confirmed the fact that gastric emptying was essentially unchanged following the procedure.

In 1975, Paul H. Jordan, Jr. of Houston presented his first paper on parietal cell vagotomy and believed that from a short-term study the operation was superior to selective vagotomy/antrectomy because of its lower rate of postoperative complications of dumping, diarrhea, and reflux. He suggested that perhaps parietal cell vagotomy might become the elective treatment of choice for duodenal ulcer but further study was necessary. Three years later before the association Jordan stated that there was now a gradual trend in America to use parietal cell vagotomy over gastric resectional procedures for treatment of the intractable duodenal ulcer. Again in 1986 he presented a splendid prospective randomized study in-

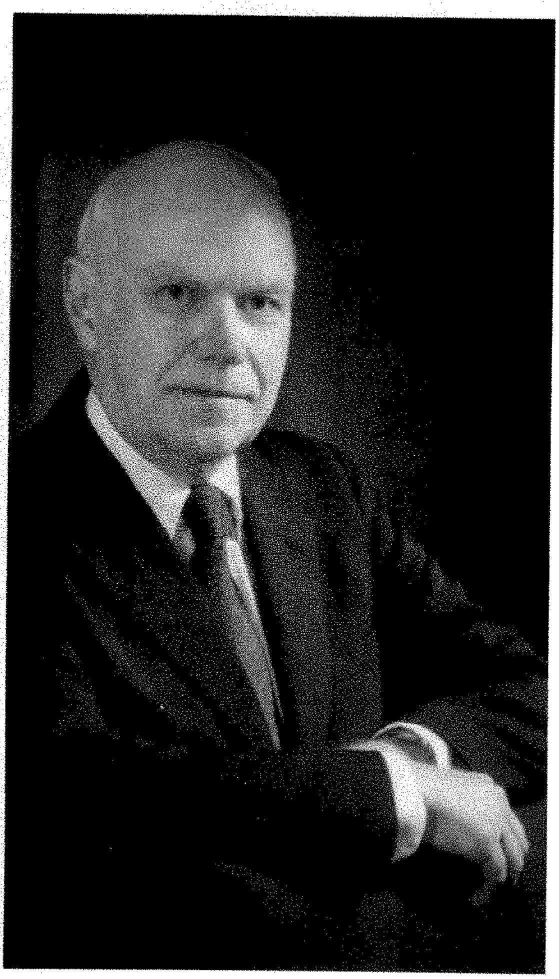


FIG. 14. John L. Sawyers, president at the centennial meeting.

volving 200 patients treated electively with either parietal cell vagotomy or selective vagotomy/antrectomy with a 10-year follow-up. This represented a monumental piece of work and rivaled any of the papers on the subject from Copenhagen and Leeds. He reported only a 6% recurrent ulcer rate using parietal vagotomy for duodenal ulcer, and long-term symptoms of dumping, diarrhea, and reflux were negligible. There were no recurrent ulcers in the selective vagotomy/antrectomy group, but significant symptoms of dumping, diarrhea, and reflux were encountered. He also believed that parietal vagotomy might be acceptable for a type I gastric ulcer, but was unacceptable for the treatment of a pyloric and prepyloric ulcer. In 1976, John Sawyers of Nashville presented 21 patients with acute duodenal ulcer perforation treated by closure and parietal vagotomy with no mortality. He believed that the procedure represented a satisfactory compromise between simple closure alone, which did not insure against recurrence, and a definitive operation as vagotomy with resection or drainage, which would subject some patients who would have no further problems after simple closure to long-range complications of dumping and diarrhea.

The 1975 meeting included a paper by Patrick O'Leary, Edward Woodward, and Lester Dragstedt of Gainesville, Florida in which they cited 455 patients who had undergone vagotomy and drainage for duodenal ulcer over a long-range period with an ulcer recurrence rate of 5.8%. Both Lynwood Herrington, Jr. of Nashville and Ward Griffen of Lexington informed the authors that 24% of patients in the Florida study had been lost to follow-up, and that perhaps their recurrences might have been as high as Griffen's and Herrington's if all patients had been followed. Griffen had previously reported a recurrence rate of 25% among 112 patients.

James Thompson of Galveston presented his first paper before the association as a new member in 1975. He spoke eloquently on the effects of gastrin and gastric acid secretion after five different operations for duodenal ulcer. He showed that vagotomy with antrectomy was the most effective operation in lowering gastric secretion. He was so happy over being elected to fellowship in the association that after his presentation he screamed aloud, thanked the association, raised his hands over his head, and gave a real rebel yell. (Thompson states that he was no relation to James E. Thompson of Galveston, the 32nd president. Jim, however, further mentions that he generally does not object to the fact that many people think James E. Thompson was his grandfather. Isidore Ravdin always thought so and Jim believes that is the reason he became chief surgical resident at the University of Pennsylvania.)

Only three papers have been presented before the association addressing the Zollinger–Ellison syndrome. At the 1978 meeting, Charles Davis and John Vansant of Norfolk cited the fascinating case of a patient who underwent total gastrectomy but later developed liver metastasis which spontaneously regressed. This was confirmed by appropriate scanning and at subsequent operation for cholelithiasis. Although serum gastrin levels continue to be elevated in the range of 1000, the patient currently remains asymptomatic after 27 years.

Although many gastric ulcers are currently being treated successfully with the H_2 receptor blockers, R. B. Adkins et al. of Nashville showed at the 1984 meeting that significant complications can occur while undergoing this medical management (Fig. 14). In a series of 163 patients, it was their opinion that medical therapy had been unduly prolonged, and among patients who came to surgery, 35% were operated on as emergencies for either hemorrhage or perforation. Lesser operations than resection were performed only in high-risk patients. Earlier operative intervention was stressed for gastric ulcer patients, and vagotomy was always added to resection in the presence of a type II (gastric and duodenal ulcers) and type III (pyloric and prepyloric ulcers.)

In 1984, Robert McClelland of Dallas discussed the treatment of recurrent ulcer after various operations on the stomach in which the original vagotomy was incomplete. Irrespective of the original operation for ulcer, if the author could show the presence of an incomplete vagotomy by the sham-feeding peak acid ratio, transthoracic vagotomy was the sole remedial procedure carried out. This rather conservative approach to the problem was in marked contrast to the more radical procedures reported by Claude Welch in former years for the treatment of recurrent ulcer.

In 1985, Hunter McGuire and Shelton Horsley, III of Richmond presented a paper entitled, "The Emergency Operation for Gastric and Duodenal Ulcer in High Risk Patients." The authors stressed the universal decline in the incidence of duodenal ulcer, but noted that they were still seeing patients in the intensive care units who required operation for perforation and bleeding. In such patients the hospital mortality rate was 14.5%. In former years the mortality among better risk patients was 2.7%. This recent increase in mortality was attributed to the presence of multiple organ disease and to the advanced age of the patients.

Summary

By the early part of this century, members of the Southern Surgical Association as well as others began to realize that gastroenterostomy alone was unacceptable for the treatment of gastric ulcer. Ulcer excision and some type of limited resection was advised. At a later date, gastric resection of varying extent, depending on ulcer size and location, became the appropriate treatment for complications of this disease.

For treatment of complications of duodenal ulcer, gastroenterostomy was widely used from the latter part of the 19th century until the late 1930s. Adequate gastric resection slowly but cautiously replaced gastroenterostomy during the 1940s. Vagotomy with drainage and vagotomy with antrectomy slowly developed and replaced adequate resection by the early 1970s. Beginning in the 1970s and extending into the 1980s, fewer duodenal ulcers were seen, and many of those encountered were being adequately managed using the H_2 receptor blockers.

For the intractable duodenal ulcer there is currently an increasing trend to use the less invasive operation of parietal cell vagotomy. Vagotomy with antrectomy for such cases is being used less frequently. Vagotomy and drainage has lost much of its appeal. Lesser procedures have been advocated recently for treatment of marginal ulcer after incomplete vagotomy irrespective of the original operation for ulcer. Massive bleeding and acute perforation are still frequently encountered as complications but are being seen more frequently in elderly high-risk patients, some of whom will tolerate only a lesser procedure as suture ligation, vagotomy with drainage, or simple ulcer closure. It appears that we are now seeing a different duodenal ulcer pattern in the good-risk patient. The ulcers are usually small, less virulent, and less likely to be found penetrating into the pancreas and adjacent organ structures. As Claude Welch so aptly stated recently before the Association, "We are seeing a trend in ulcer surgery that is currently being seen in other areas of surgical endeavors as well." He emphasized that we must be alert to changing disease patterns and adapt our procedures to new requirements.

Acknowledgments

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Plastic Surgery

The First 100 Years of the Southern Surgical Association

M. J. JURKIEWICZ, M.D.

From the Department of Surgery, Emory University School of Medicine, Atlanta, Georgia

WHEN I WAS ASKED to recount the first century of plastic surgery in the Southern Surgical Association (SSA) I accepted with both anticipation and pleasure.

Rather than take a strictly taxonomic approach I will attempt to be more personal. In so doing I wish to make three general points and illustrate these with specific examples within five eras in the past century. (1) It has always been my belief that plastic surgery is part and parcel of general surgery—no more, no less. (2) Beliefs are shaped by our teachers and our traditions. (3) The SSA has had a unique role in the development of plastic surgery.

The belief that plastic surgery is an extension of general surgery clearly did not originate with me. It was impressed upon me in countless ways by my chief at Washington University and Barnes Hospital, Carl A. Moyer. He strongly believed that there is a core of knowledge that all surgeons of whatever discipline should possess. For plastic surgery that core was full training in general surgery. His conviction was born not only of the intuitive faith of surgeons but also his experience at Michigan, Dallas Southwestern, and especially by what he saw and learned at Barnes Hospital in St. Louis.

In 1951 he succeeded Evarts A. Graham as chief of surgery at Barnes Hospital. Graham at that time was the most powerful figure in American surgery. He organized the founding of the American Board of Surgery; he put intellectual spine into the American College of Surgeons; and was chairman of the Board of Regents at the time. Graham, who was appointed as Chairman of the Department of Surgery at Washington University in 1919 while on terminal leave from the Army, appointed Vilray Papin Blair as chief of plastic surgery at Barnes Hospital. Blair in turn, with Graham's help, organized and founded the American Board of Plastic Surgery as a subsidiary board of surgery in 1937.

Some of the men that Graham trained in surgery were picked by Blair to be trained subsequently in plastic surgery. They became the staff at Barnes Hospital, and in Moyer's time the unit led by James Barrett Brown and Louis T. Byars was by reputation the best in the country. Thus, the tradition and the belief that plastic surgery was an extension of general surgery was firmly established at Barnes Hospital at Washington University.

When Blair was speaking throughout the country to gain support for the establishment of the American Board of Plastic Surgery, his message was twofold. Plastic surgery, overall, was ill done because of ill training. The remedy lay in national standards of training and education with a strong background in general surgery. His belief can be summarized in these statements. "I feel strongly, and have so advised all younger men seeking advice, that in its future development plastic surgery will reach its greatest usefulness, its widest application, and bring the greatest personal return when it is studied and practiced as a division of general surgery."[1]

"The term general as applied to a surgeon indicates neither the quality of his work nor the extent of his endeavors, but implies a basic grasp of medical and surgical principles that will permit development along any chosen line of practice, with also a dominant concern for the activities and wellbeing of the body as a living and acting unit."[1]

Presented at the 100th Anniversary Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 6–9, 1987.

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The Southern Surgical Association's Unique Role

In the SSA plastic surgery was developed by men who were general surgeons with a special interest in plastic work. Their orientation firmly established the character of the discipline not only within the Association but also nationally. Plastic surgery continues to be strongly identified with general surgery to this day and there is every indication it will continue for the foreseeable future.

That development within the SSA is unique and is directly explicable by the historical events of the time. Many if not most of the founding and early members of the SSA augmented their surgical training by extensive periods of time in the major centers in Europe—London, Vienna, Paris, and Berlin. In each of these centers men such as Czerny, Billroth, Butlin, and Lane were performing operations to correct congenital malformations including cleft lip and palate, skin grafting, flap surgery (as it was understood in those days), and operations for cancer of the head and neck. These skills so learned became part of their general surgical practice upon return to this country.

At the same time that the South was struggling under reconstruction the rest of the country was experiencing a great wave of immigration, much of it from eastern Europe to the northeastern industrial cities. For example, by the turn of the century New York was transformed into a city composed of four-fifths recent immigrants and first generation Americans by the turn of the century. Coming in on this wave of immigration were practictioners of medicine of all sorts including self-designated surgeons of uncertain background and training whose practice was largely that of facial cosmetic surgery, such as it was. Plastic surgery outside the South therefore, developed in a diverse way—from bona fide general surgeons with a specific interest in reconstructive work to outright entrepreneurs, charlatans, and quacks.[2] By contrast, plastic surgery within the SSA developed purely as a general surgical discipline. The leaders of plastic surgery within the SSA were also the very men who played key roles in the establishment of standards of education and training as well as the specialty board of plastic surgery itself.

The Early Years, 1892–1911

The first paper on a plastic surgery subject presented at the SSA was given by William Perrin Nicolson in 1892.[3] In 1894, Nicholson gave a paper on the treatment of congenital nevi (hemangiomas). J. T. Wilson described plastic operations in carcinoma of the breast. In 1894, Long maintained that the three essentials in successful abdominal work were asepsis, hemostasis, and plastic work.[4] By that he meant the use of peritoneal flaps to cover all raw surfaces and to reperitonealize the pelvic floor. He thought that this would prevent morbid adhesions and that such "plastic work contributed materially to asepsis and hemostasis."[4] He acknowledged, however, "Of course, if the case is septic, no amount of plastic work, however beneficial, can do away with the necessity of drainage."[4]

During the next 3 years Edmond Souchon wrote articles on a device to deliver uninterrupted anesthesia in operations on the face and mouth; on the peculiarities of the surgical diseases and injuries of the neck; and on diseases and injuries of the face. He subsequently presented a paper on the diagnosis and operative treatment of tumors of the maxilla. He recognized at this early stage of the development of head and neck cancer surgery the necessity of stabilizing not only the anterior mandible but also of properly reconstructing the geniohyoid mechanism to facilitate breathing and swallowing after extirpation of lesions of the anterior floor of the mouth.

Two papers on cleft lip and palate by James E. Thompson appeared in 1899 and 1911. In that same period there was another paper on the subject by Alex Hugh Ferguson. The operations for repair of both cleft lip and palate were well established by that time and differed little in principle. However, as described by Thompson these operations were exquisitely exacting exercises in "mathematically accurate" measurements as a guide to repair. These articles by Thompson as well as a subsequent one given at the SSA meeting in 1921 were recognized as classics in the field.[5]

The first paper on skin grafting appeared in 1909 by Arthur Scott, who described his method of Thiersch skin grafting and added the technique of meshing the graft. This was less than two decades after Carl Thiersch had presented his technique for cutting sheets of epidermis with a very thin portion of dermis at the German Surgical Congress.

Other contributions in that early period included a paper on hypospadias and epispadias by F. W. Parham, who today is remembered for Parham bands, a method of fixation of long bone fractures. Southgate Leigh described a repair of the base of the bladder by a plastic operation (perineal flap). Alex Ferguson presented a paper on vaginoplasty for congenital abscence of the vagina. Finally, there were two papers on reconstructive rhinoplasty: one by E. Denegre Martin and the other by J. M. T. Finney. In that paper Finney described a novel method of using the little finger to provide bony support for the dorsum of the nose.

Two Future Presidents of the Southern Surgical Association, 1911–1938

The period that roughly included World War I and the years up to World War II was dominated by two

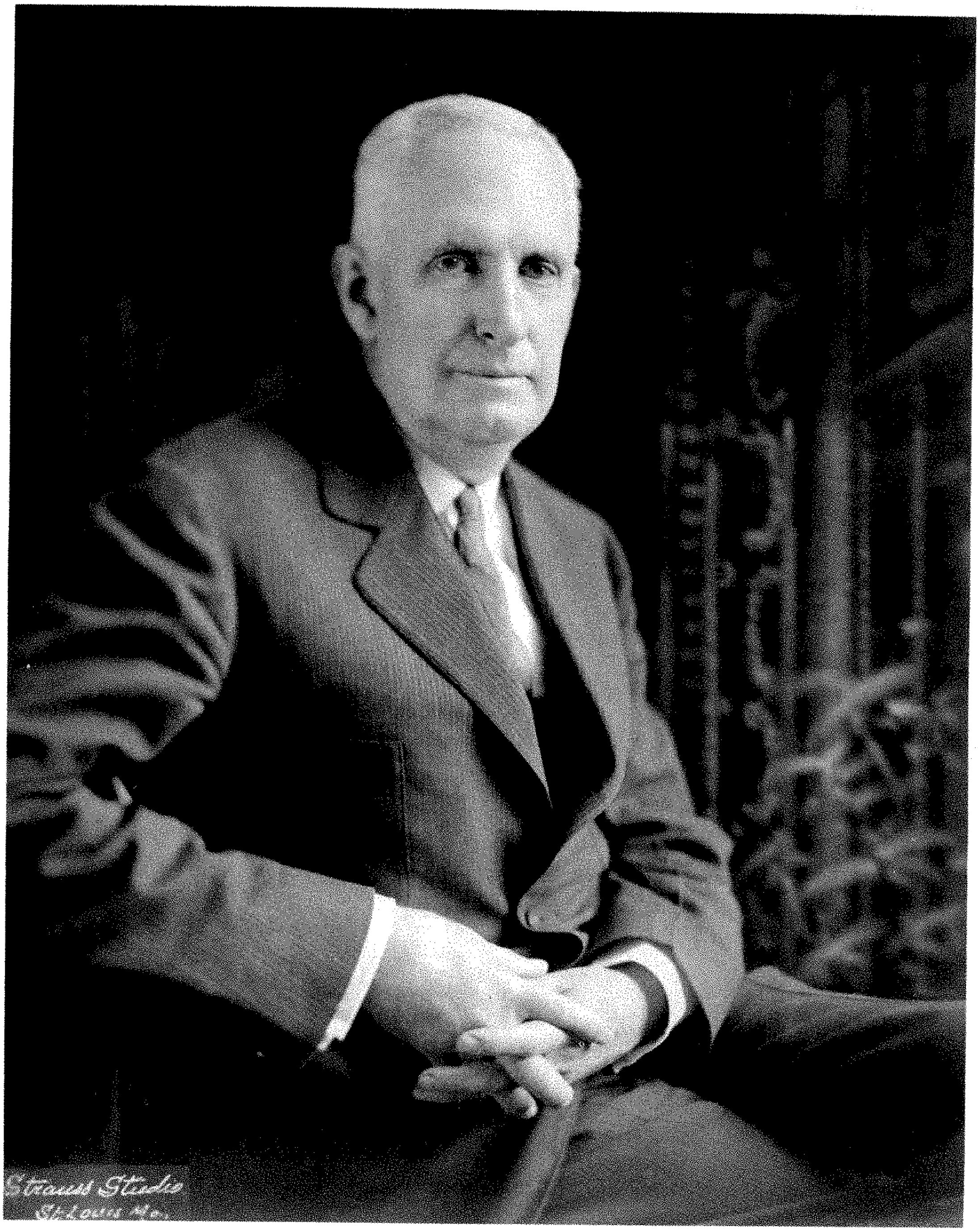

FIG. 1. Vilray Papin Blair.

men: Vilray Papin Blair (1871–1955) (Fig. 1) and John Staige Davis (1872–1946) (Fig. 2). These two men more than all others shaped the destiny of plastic surgery as a specialty. They were the first individuals in this country to devote most, if not all, of their work to plastic surgery. They insisted on identical standards of broad training in general surgery to be followed by training in plastic surgery. Both men were associated with chiefs of surgery who were the dominant figures in American surgery of their time—Halsted and Graham. There is an enduring legacy to American surgery by both Blair and Davis. Blair did so through the men he trained on a distinct and identifiable plastic surgery service at Washington University. Davis participated in the training of a long list of resident house officers in surgery at Hopkins where he was in charge of plastic surgery from 1923 until a brief period prior to his death. Some of these men went on to become chiefs of plastic surgery, for example, Kenneth Pickrell at Duke. Davis, however, was never allowed to establish a distinct specialty service at Hopkins as did Blair at Barnes Hospital.

Both men were enormously influential in the development of reconstructive surgery to the wounded in World War I. Both were instrumental in the establishment of the American Board of Plastic Surgery. Davis was the first chairman and Blair, the first secretary. Blair held that post for many years and the secretary's office remained in St. Louis until 1979 when it was moved to Philadelphia with the American Board of Surgery.

In 1911 Davis presented his first paper to the association, a report on the repair of a cheek defect by a lateral arm flap. His opening remarks in that paper constitute a three paragraph homily that sums up his thinking about the field: "Plastic surgery is attempted by almost everyone who undertakes surgical work and I do not know of any class of cases which is more frequently botched. The scope of this branch of surgery is very broad and includes nearly every region of the body." "A thorough general surgical training is necessary before this work can be properly done. Ingenuity, patience, and constant personal supervision are required."[6]

In 1912, Blair produced a discussion of the paper by Martin on fixation and repair of fractures of the femoral neck. He made his point on plating of fractures in general by citing his broad experience in fractures of the jaw. In 1915 Blair presented his extensive experience on the treatment of cleft lip and palate. In that article he described and illustrated his variation of the cleft lip repair, which became the standard in the country until the late 1950s when it was superseded by the rotation advancement repair described by Millard. Davis presented a paper on the use of free grafts of full thickness skin for the relief of contractures. A hiatus in presentations to the SSA followed because of World War I.

After the entry of the United States into the war, Blair promptly volunteered his services. Commissioned as a captain and assigned to Fort Oglethorpe, Georgia, in June 1917, he was elevated to major later that year and transferred to the Office of the Surgeon General of the Army as Chief of the Section of Oral and Plastic Surgery. Blair was credited not only with the organization of such a service but also the competent care of American soldiers with wounds of the face and jaws so prevalent in the trench warfare of World War I. In this work he was assisted greatly by Dr. Robert Ivy of Philadelphia.

Blair went to England and France in 1918 as chief of the section and took an active part in the battle of Chateau-Thierry and the Argonne. After the war he established centers for oral and plastic surgery throughout the country within Veterans Hospitals. Davis served as Captain in the Medical Corps of the Army from June 1917 to January 1919 and in World War II was a special consultant to the Surgeon General of the Army.

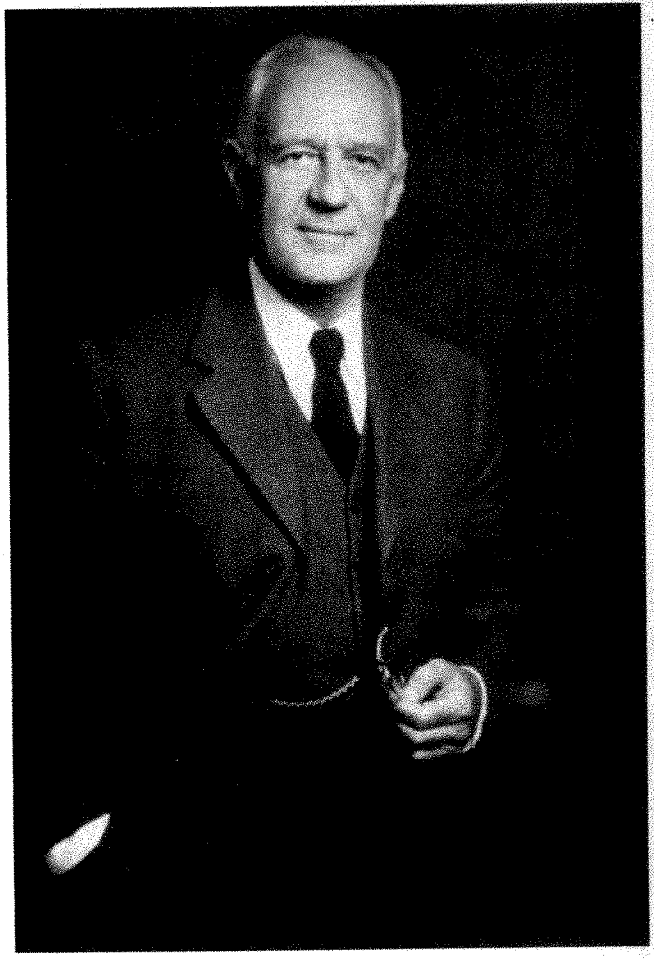

FIG. 2. John Staige Davis.

In 1921, Blair gave a paper on saddle nose of luetic origin. In 1924 he updated his experience on cleft lip repair. In 1926 he described the pathophysiology and psychology of the deformed face. In 1928 and in 1932 he presented two landmark papers on the use of large split skin grafts of intermediate thickness. The first of these was coauthored by James Barrett Brown and the second by Brown and William Hamm. These were telling descriptions of thick split grafts used as broad sheets cut by a freehand knife. These two papers changed forever both the thinking and the techniques of skin grafting. At the 44th annual meeting of the SSA, he presented a paper that described room 8 at Barnes Hospital, the walls of which were painted with animals and scenes from fairy tales designed to allay the fears of children. I am advised that this is one of the very rare instances in a paper that was actually presented at a meeting was not published in the Transactions. Blair's career as a plastic surgeon was capped by election to the presidency of the SSA in 1933.

He retired from active practice in the mid-1940s and died in 1955.

In the year of Blair's presidency, John Staige Davis gave a detailed physiologic study that he carried out with Edward A. Kitlowski on regeneration of nerves in skin grafts and skin flaps. They documented the rate of return of protective sensation in flaps, full thickness, and partial thickness grafts in that order. They also described a dissociation of the sensations of pain, temperature, and touch in all types of transplants and the reappearance of these sensations in the order named.

During those years Davis also presented papers on general plastic surgery, x-ray burns, Z-plasty for the relief of scar contracture, and a description of plastic surgery in World War II. He was elected president of the Association in 1940 and died in 1944, one month after he had been elected to the Board of Regents of the American College of Surgeons.

From 1914 to 1938 these two men, Blair and Davis, presented 19 papers to the Association. In addition, during those roughly three decades six papers were presented by other surgeons interested in the field of plastic surgery. One of these was by J. Shelton Horsley of Richmond who unfortunately died an untimely death in 1940 at the age of 41. Shortly before his death he had been made Professor of Oral and Plastic Surgery at the Medical College of Virginia. His papers before the Association were entitled "Plastic Operations for Acquired Deformities of the Face" and "Surgical Treatment of Extensive Basal Cell Carcinoma." Had he lived he might have rivaled James Barrett Brown who dominated plastic surgery from 1940 until his retirement in 1968.

The Mantle of Leadership Passes, 1938–1963

Over the next 25 years the kingpin of plastic surgery in the SSA and arguably in the country was James Barrett Brown. Trained by Evarts Graham and Vilray Blair, Brown in 1941 was named consultant in plastic surgery to the Surgeon General. This was the same post held by Blair in World War I. Colonel Brown and Major Bricker organized plastic and reconstructive surgical care for the wounded both in the European Theatre of Operations and in the Zone of the Interior. The story of that remarkable achievement was documented in the *Transactions of the Southern Surgical Association* by John Staige Davis. During the war years Brown presented papers on composite grafts to reconstruct the nose as well as various methods of handling war wounds. In 1949 he presented a paper on congenital torticollis; hemangiomas in 1952; penoscrotal skin losses in 1956; and his last paper in 1962 which was on the use of alloplastic substances in reconstructive surgery of the facial skeleton.

Louis T. Byars, an associate of Brown at Barnes Hospital, gave his first paper to the SSA as a coauthor with Blair in 1938. It was a description of a remarkable toe to finger transplant. Byars was a most thoroughly ambidextrous surgeon. He presented a paper on skin grafts and flaps in 1944. In 1947 he described his extensive experience in the reconstruction of the mandible following head and neck surgery. These two men, Brown and Byars, brought plastic surgery to its full potential as a teaching service at Barnes Hospital for the postgraduate education of plastic surgeons in the 1950s and early 1960s—a legacy of Blair.[7] Byars was the first plastic surgeon to actually serve on the Board of Regents of the American College of Surgeons.

In that same period there were papers by Truman Blocker on the application of techniques of reconstructive surgery to certain problems in general surgery; cleft palate repair by Gordon T. McCutchen; and malignant melanoma by William McCune and Gordon Letterman. In 1954 Murray Copeland described his technique for neck dissection in the treatment of cancer of the head and neck. In the following year Robert L. Payne gave a paper on the use of skin grafts in radical mastectomy and Kenneth Pickrell described the use of the gracilis muscle as a transplant to correct urinary incontinennce in male children.

Cross finger flaps was presented in 1956 by Raymond Curtis, and in that same year Eugene Bricker and Thomas Burford presented their experience with tubed pedicle grafts in reconstruction of the esophagus. Henry Royster presented his experience with malignant melanoma.

Two years later William McFee described his technique for repair when major portions of the lower lip had been resected. That same year Meredith Alrich and Lee Brown of Charlottesville, Virginia gave a paper on their experience with cancer of the tongue. In 1958 Blocker presented the studies he conducted with his colleagues on lymph flow in lower extremities of patients with chronic ulceration and edema. In 1959 Curtiz Artz and Benjamin Gaston described the exposure method of handling burns in donor sites, and 3 years later Joseph Hamilton described fascia lata free grafts in the repair of large hernias.

The Legacy of World War II and Korea, 1963–1971

Men of this era were trained in plastic surgery during World War II or the Korean conflict in centers such as Valley Forge commanded by James Barrett Brown in World War II. In this decade there were papers on the surgical treatment of extensive cancers of the mouth and pharynx by Claude C. Coleman, Jr., chronic cystic parotitis by Truman Blocker et al. Coleman presented another paper to the SSA in 1965 on pedicle flaps in reconstructive surgery of the hand. Replantation of amputated extremities was presented by G. Rainey

Williams in 1965. In 1966 Milton T. Edgerton described his method for the surgical correction of facial paralysis. In 1968 B. W. Haynes presented his work on the early excision and grafting of third-degree burns. In 1969 Erle Peacock described treatment of burned hands, and the following year, Bert Myers and Isadore Cohn presented their work on the prevention of skin sloughs in radical mastectomy. That same year Erle Peacock presented another paper, this one on transplantation of finger tips. The following year there were papers by Curtis Artz on allografts and xenografts as biologic dressings and a paper by Edward Krementz and Robert Ryan on perfusion of extremity melanoma.

Centers of excellence in plastic surgery were established in roughly this era at Johns Hopkins under the leadership of Milton T. Edgerton, at Duke by Kenneth Pickrell, at Galveston by Truman Blocker, at Chapel Hill by Erle Peacock, at the University of Pennsylvania by Henry Royster, and at Tulane by Robert Ryan. Each of these men was directly trained or partially trained by John Staige Davis, Vilray Blair, or their pupils (*e.g.*, Robert Ivy, James Barrett Brown, or Neal Owens).

The Century Completed, 1976–1986

The last decade of the first 100 years of the SSA is witness to plastic and reconstructive surgery by the use of musculocutaneous flaps, omentum, and free flap transfer by microsurgery. With these advances came the observations of the true nature of blood supply to skin and the technical refinements in instrumentation that made microsurgery possible.

Once again one can trace the influence of John Staige Davis and Vilray Blair directly to the developments of the modern era of plastic surgery. The concept of general plastic surgery championed by Davis and the idea that plastic surgery would best flourish as part of general surgery articulated so forcefully by Blair is exemplified by the papers at the SSA in the last decade of the first 100 years. Examples include the extracelomic use of omentum either as a free flap or as a transposition flap in reconstructive surgery, breast reconstruction following mastectomy for cancer, microsurgical composite tissue transplantation, muscle flaps in the treatment of the infected median sternotomy wound, free jejunal grafts to reconstruct the cervical esophagus, chest wall reconstruction, and the reconstructive surgery necessary to treat morbid complications of conservation treatment of breast cancer. These papers are examples of the prophetic insight of Vilray Papin Blair in his presidential address to the SSA in 1933 when he said, "With the exception of those dependent upon some more recently contrived instrument of precision, or some development in an extraneous science, there are few outstanding attainments in any surgical specialty not the direct outgrowth of its inheritance from the general surgeon."[8]

Acknowledgment

The author acknowledges the great help of Sue Ann Weber, R.N., in the preparation of this historical review. She was of great help in the identification of articles or discussions in the *Transactions of the Southern Surgical Association* that were pertinent to Plastic Surgery. Many thanks for your kindness.

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Comment from President Sawyers

Dr. Jurkiewicz's superb presentation has described the important contributions to the specialty of plastic surgery from Fellows of the Southern Surgical Association during the past hundred years, but Josh Jurkiewicz has modestly omitted his own contributions, which have been numerous. Dr. Jurkiewicz has been a frequent contributor to the scientific program of the Southern Surgical Association. I would be remiss not to call the audience's attention to Dr. Jurkiewicz's important contributions to his specialty of plastic and reconstructive surgery. He won the Shipley award for his presentation as a new member in 1976.

Dr. Jurkiewicz's presentations:

1976 The Omentum: An Account of its Use in the Reconstruction of the Chest Wall
1979 Infected Medial Sternotomy Wound: Successful Treatment by Muscle Flaps
1980 Management of Acute Full-thickness Losses of the Abdominal Wall
1981 The Omentum: Its Use as a Free Vascularized Graft for Reconstruction of the Head and Neck
1983 Pharyngoesophageal Stricture and Fistula: Treatment by Full Jejunal Graft

Transplantation of Tissues and Organs

Review of the First 100 Years of the Southern Surgical Association

JAMES D. HARDY, M.D., F.A.C.S.*

THE INVITATION to review the transplantation papers delivered before the Southern Surgical Association (SSA) over this first century has proved to be a rewarding experience. First, it has been most interesting to note the transplantation reports given successively before our society, concomitant with the worldwide development of transplantation science. Secondly, the volume by volume examination of the *Transactions of the Southern Surgical Association* over the past 100 years has given me a far wider and deeper knowledge and appreciation of the vast dimensions and the rich history of our heritage.

A review of this type poses a variety of challenges. First, exactly what constitutes transplantation? For example, blood transfusion? Or should all papers selected involve vascular anastomoses? Certainly not. However, should routine split-thickness skin grafting be reviewed? I decided not. Clearly, there has had to be some degree of selectivity in papers included for this review, but almost all are cited or appear in the bibliography. Finally, this writer is fully aware that the papers presented before the SSA represent but a very small segment of the work being published concurrently in the field of transplantation throughout the world. Space simply has precluded my giving detailed credit and priority to the many other investigators.

Next, having perused the 100 years of SSA programs, and having assembled the pertinent articles, how should the material be handled? Should the articles be taken up within rigid chronological order? Or should the papers be grouped under organ systems, with the first paper in each established field of transplantation—immunology, storage, endocrinology, kidney, heart, *etc.*—highlighted?

From the University of Mississippi Medical Center and the Veterans Administration Medical Center, Jackson, Mississippi

In the end, it was elected to group the three earliest transplantation publications as a spectacular entree, but thereafter to achieve thoughtful order by grouping the pertinent papers under specific sectors of transplantation science or specific organ transplantation (Table 1).

The First Three Reports

On the Treatment of Hemorrhage by Direct Transfusion of Similar Blood

At the 1906 meeting in Baltimore, a remarkable report was given by George Crile of Cleveland, regarding the transfusion of three patients.[7] In brief, the related donor and recipient were placed head to foot, with the right arms lying side by side on an intervening table (Fig. 1). The radial artery of the donor was mobilized and divided, the distal end ligated, and the proximal end anastomosed to the central end of the divided median basilic vein of the "donee"—after "the work of Carrel, his predecessors and associates."[7] Her son was the donor for the first patient, a 54-year-old woman with long continuing melena and a red cell count of 1.2 million and 12% Hgb. There was no reaction to the transfusion.

The first donor for the second patient, a man post-nephrotomy for stones, was a brother. Again, there was no transfusion reaction. The physical appearance and blood laboratory values of the recipient improved dramatically, and a nephrectomy was performed. However, subsequent hemorrhage required direct transfusion from another brother. This time, in contrast, the donee complained of precordial distress and protested loudly that he felt sick. His breathing was markedly increased. "Later, he was seized with a chill accompanied by considerable circulatory disturbance."[7] The patient gradu-

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ally regained his composure and was much improved. There was no further bleeding and the patient recovered.

The third patient had anemia associated with gallbladder cancer. The patient's brother served as donor and there was no reaction. Nevertheless, after the continuous flow had been maintained for 40 minutes, the donor showed "slight evidence of fainting" and the transfusion was terminated.[7] [The Riva-Rocci sphygmomanometer had been brought to the United States by Harvey Cushing in 1901. Crile knew the instrument but it was not used here.] Interestingly, during the transfusion, bleeding from the patient's nose and uterus, which had been progressive, ceased.

What profound hazards had lurked, during these daring, epochal and beneficial transfusions: donor shock from unmeasured blood loss to the donee and anaphylactic transfusion reaction in the donee due to incompatible blood. Yet, Crile clearly knew that a close relative would be the best donor. [Landsteiner in Germany had presaged the ABO blood groups in 1900, but routine matching was yet to be developed.] And one may speculate that the platelets and fresh plasma transfused may have corrected the coagulopathy and stopped the spontaneous nose and uterine bleeding in the third recipient. [Apparently, William S. Halsted had performed the first transfusion in the United States, in 1881, from himself to his sister, using a syringe.]

J. M. T. Finney of Baltimore was asked to open the discussion. He congratulated the essayist and expressed the hope that Crile would demonstrate his method on a dog before the members of the Society. He suggested that Dr. Cushing would be willing to help in making the necessary arrangements. [Cushing was then in charge of the surgical "dog lab" at Johns Hopkins.] Finney asked why a cannula could not be used between the artery and vein to simplify the procedure. Crile replied that they had tried a variety of cannulas in animals, but that the clotting problem was too great. Samuel J. Mixter of Boston believed that Crile had been too modest. Why not tranfuse prophylactically?: "We all know the terrible, uncontrollable hemorrhages that occur after operations during deep jaundice, and which, at present, in spite of giving various agents, have proved so intractable."[7] [Note the bleeding hazard of surgery in the jaundiced patient prior to the discovery of vitamin K.]

Robert T. Morris of New York asked why there had not been more hemolysis in Crile's three patients. He also noted that "in our grafting work, in transferring tissues from one animal to another, there is a well-known principle of intolerance, and this must apply with extreme force in a case where blood carried from one individual is to be taken by the blood of another individual."[7]

William H. Welch, pathologist was asked to take part in the discussion. He reviewed the history of blood transfusion, noting that "in the seventeenth century it was supposed that one of the greatest discoveries in practical medicine had been made in the transfusion of blood." As regards renal hemorrhage in one of the cases, he asked "whether Dr. Crile has had any experience in the administration of kerosene, and whether it is useful or not in these cases?"[7]

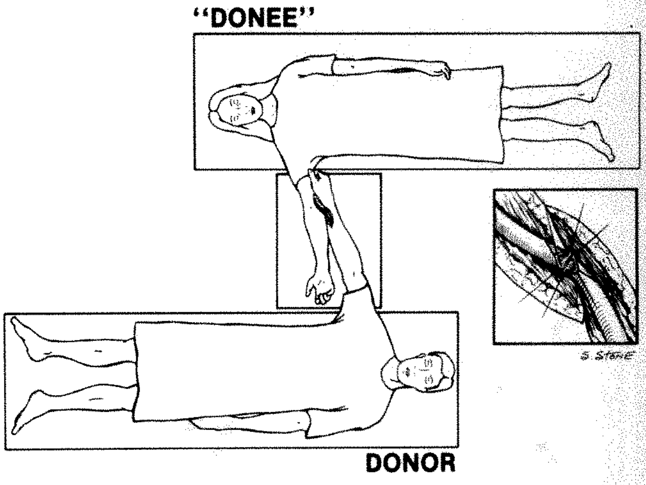


FIG. 1. Artist's conception of the positioning used by Crile for direct blood transfusion. The proximal end of the radial artery of the donor was anastomosed to the central end of the divided median basilic vein of the "donee" (Crile's designation).[7]

Report of a Case of Urethral Transplantation (1908)

At the 21st session in 1908 in St. Louis, J. D. S. Davis of Birmingham presented a preliminary report on the operation for transplanting a calf's urethra (4 inches) into a man whose perineum had sloughed.[9] Davis said, "A young calf was killed by my butchers at 4 A.M., and its entire urethra and bladder dissected out and put in cold normal salt solution and sent to the hospital to be used at 8:30 A.M. I was detained in an important emergency case and did not reach the hospital until my regular clinic hour—2 P.M., ten hours after the calf was killed."[9] "I sent two of my internes, Harris and Lanier,

TABLE 1. *The Sequence of Major Headings**

1. Three Earliest and Spectacular Publications
2. Orthopedics Transplantation
3. Endocrine Transplantation
4. Allotransplantation Biology
5. Skin Transplantation
6. Kidney Transplantation
7. Biliary and Alimentary Tract Transplantation
8. Lung Transplantation
9. Vascular Transplantation
10. Microvascular Transplantation
11. Valvular and Total Heart Transplantation
12. The Multiple Organ Transplant Program

* There have been no reports dealing with liver transplantation.

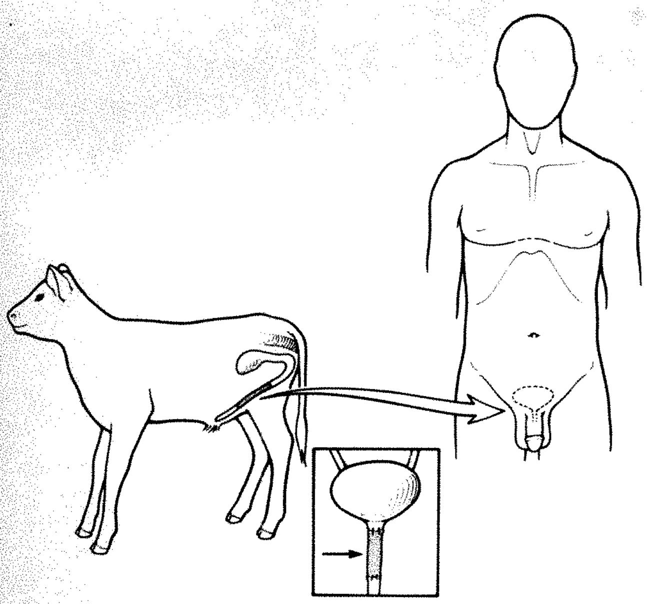


FIG. 2. Artist's conception of Davis' procedure for transplantation of calf urethra.[9]

to make the dissection from the calf under sterile precautions, but they did not reach the slaughter house before the butcher had removed the specimen". . . . "When I had the field ready, I passed a rigid rubber catheter (No. 30 F.) through the pendulous urethra, through the four inches of the calf's urethra, and then through the prostatic urethra into the bladder." (Fig. 2).[9] The catheter was removed on the tenth day. The suprapubic syphon drainage was discarded on this date and a No. 20 F. sound was then passed, being used daily for five times, and then every second day for six times. Twenty-one days after the operation an unsuccessful effort was made to close a fistula at the distal end, but a biopsy of the heterograft taken at that time and examined microscopically exhibited no changes. The patient was well and the fistula had closed over a year later.

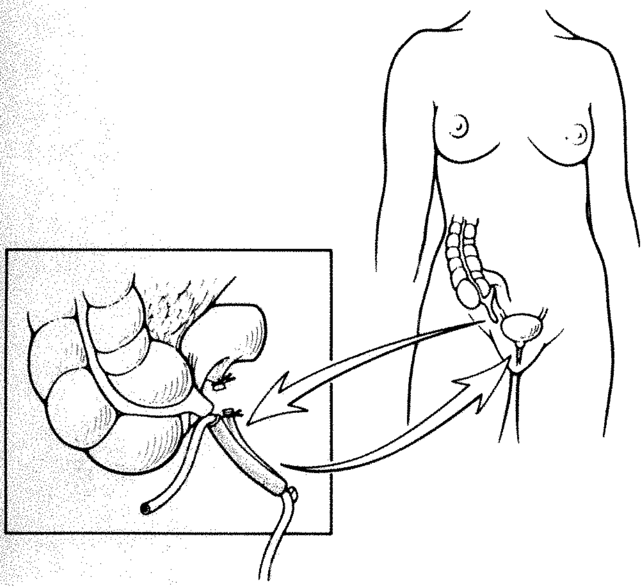


FIG. 3. Artist's conception of operative technique used by Rosser for urethral repair using appendiceal autotransplantation.[39]

One can only speculate regarding the possible survival of the heterograft, on the one hand, and on the possibility of auto-urethral mucosal generation to replace a disintegrated heterograft (xenograft), on the other hand.

Transplantation of the Appendix to Supply an Absent Urethra (1918)

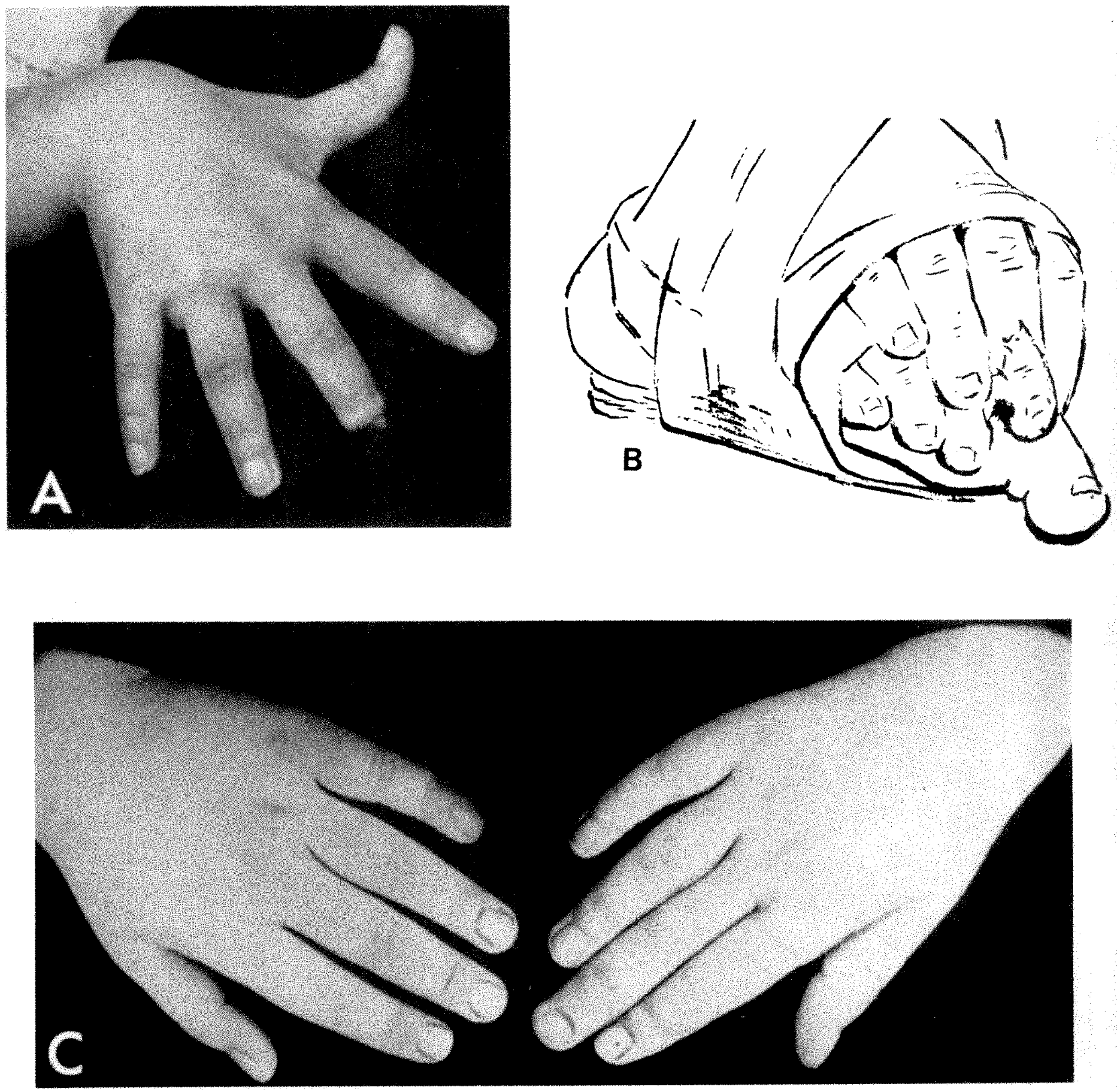
Rosser at the 31st meeting in 1918 in Baltimore, described a patient in whom her own appendix had been used to replace her urethra (Fig. 3).[39] The follow-up evaluation was only a few weeks at the time of the meeting, and the ultimate fate of the appendiceal transplant used to replace her cancerous urethra is unknown. The principal discussor was Guy LeRoy Hunner, of Baltimore, who described Hunner's ulcer of the bladder.

Orthopedic Transplantation

One of the most striking aspects of the history of transplantation in the SSA is that early on the current subspecialties were still largely within the domain of the general surgeon: urology, gynecology, and orthopedics especially. Thus, earlier in our history, papers dealing with problems in these subspecialties were commonly presented at our annual programs. And so it was with orthopedics.

At the 1912 meeting Baer presented his paper "Arthroplasty with the Aid of Animal Membrane" in which he reviewed experimental results in dogs and presented results in 100 patients, some followed for up to 8 years.[3] In brief, he used chromicized pigs' bladder as the material of "interpolation." He believed that this absorbable material, which did not disintegrate until from 60 to 100 days, preserved joint space and motion, while surrounding tissue provided a new fibrous covering to be formed on the surfaces of the joint. The pig membrane was kindly prepared "by Messrs. Johnson and Johnson."[3]

At the 1918 meeting Martin presented a paper and stated that, "probably no class of cases occurring in the recent war has offered more important and interesting problems for solution than *gunshot fractures of long bones.*"[27] The fractures were commonly complicated by sepsis and osteomyelitis, and often as well by nerve in-



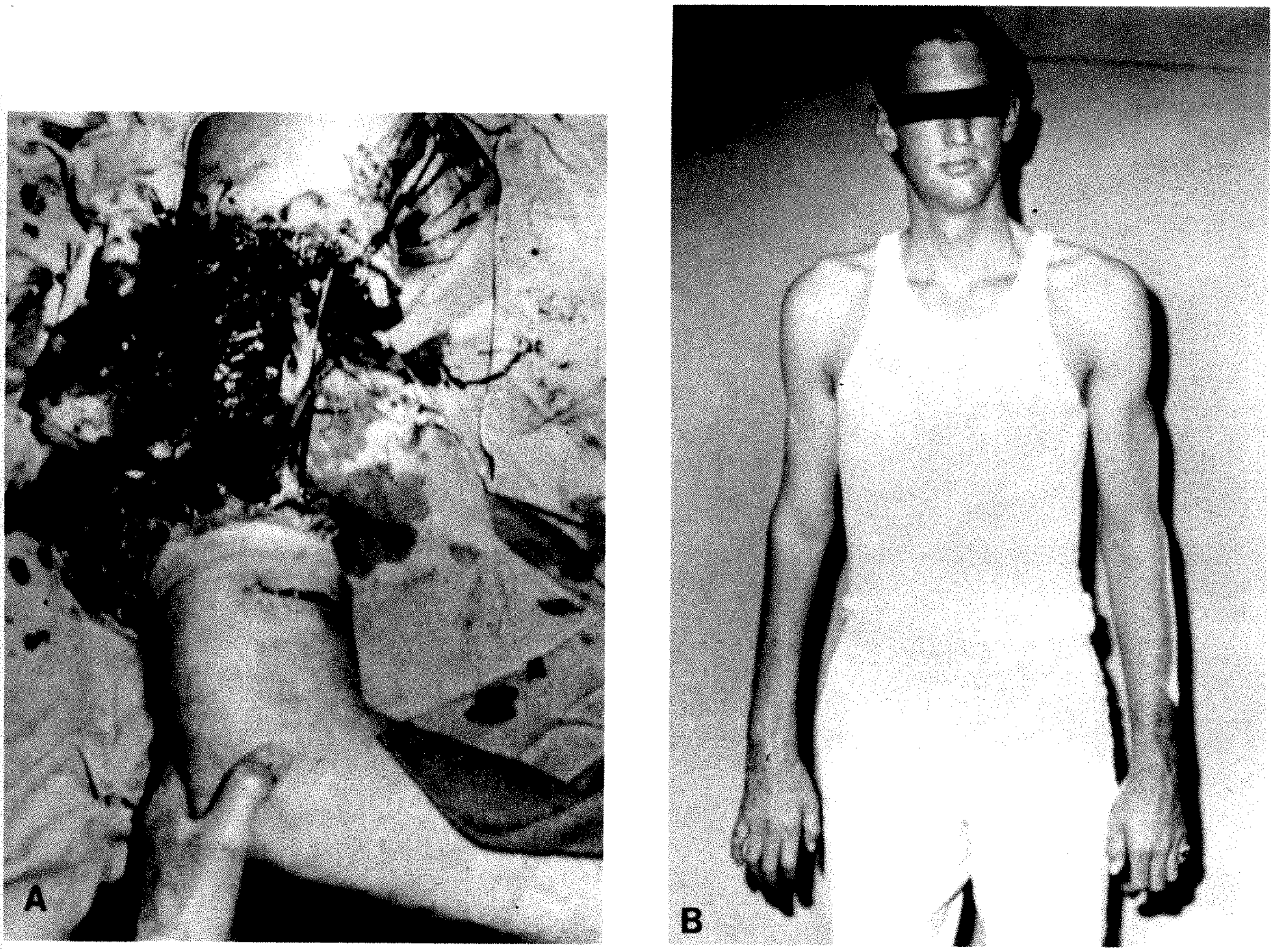
FIGS. 4A–C. *A.* Severed tip of the right middle finger. *B.* Distal phalanx of right middle finger sutured to distal phalanx of the right second toe. *C.* Excellent cosmetic result.[4]

jury, but the bone grafts were considered beneficial in most of the patients.

Another bone transplantation report was that in 1944 by Blocker and Weiss.[5] As Martin's report had dealt with his experience in World War I, Blocker and Weiss's report dealt with their experience in World War II.

The bone autotransplants did not require preservation of continuous blood supply immediately after transfer. However, now the transplant horizons began to include consideration of transplanting tissues the blood supply of which had to be preserved for success. Using the full thickness pedicle skin flap, Blair and Byars of St. Louis, at the 1939 meeting, discussed a case in which the tip of the right middle finger of a young girl had been reconstructed using the distal phalanx of the right second toe.[4] As shown in Figure 4, the cosmetic result was excellent. Peacock et al.[34] also reported their work with transplantation of fingertips at the 1970 meeting.

Even so, the aforementioned finger transplants still had not required formal vascular anastomoses. However, "shortly after midnight, on November 1, 1964, a 20-year-old white male college student was admitted to



FIGS. 5A and B. *A*. Severed right arm. *B*. Reimplanted right arm months later.[49]

the University of Oklahoma Medical Center following amputation of the right upper extremity."[49] Former president G. Rainey Williams, in collaboration with Carter, Frank, and Price, replanted the arm successfully, as shown in Figure 5.[49]

While parts of extremities had been replanted clinically previously, this case constituted a signal achievement, and in the years since then extremity replantation has become commonplace.

Endocrine Transplantation

Endocrine transplantation did not require the sophisticated use of vascular anastomoses, and hence the early endocrine studies preceded clinical transplantation of whole organs such as the kidney, lung, and heart.

Although William S. Halsted of Baltimore was never a member of the SSA, his earlier work probably was seminal in the field of endocrine autotransplantation and homotransplantation. The first mention of endocrine (here, parathyroid) transplantation (implantation) before the SSA appears to have been that of Mayo and McGrath in their paper: "the surgeon should scrupulously guard against removal or injury of the parathyroids. . . . If such a mass be accidentally removed in the course of operation it should be at once implanted beneath some part of the remaining capsule."[28]

Nonetheless, by far, our earliest and most persistent SSA endocrine transplanter was Stone[45–48] of Baltimore, whose first related paper, "Living Grafts of Endocrine Glands," was presented at the Hot Springs meeting in 1933.[48] He and his colleagues had transplanted parathyroid tissue and thyroid tissue to other sites in the same dog and to other dogs, employing many ingenious variations and gaining extended survival in some instances. They acknowledged "the general feeling among medical men that it is impossible to graft successfully living tissues from one animal to another". . . . They noted "the general feeling that this represents some antagonistic chemical action, perhaps like an allergic phenomenon because of incompatibility between the biological chemistry of the graft and of its host."[48] They also transplanted human parathyroid on two occasions in a female patient, after growing the allotransplants for a period of time in the prospective recipient's serum. Complete reversal of the patient's hypocalcemia (4.9 to 6.6 mg/dL before operation) and the relief of chronic tetany were achieved. However, the follow-up time was only 5 months. [It is well known that parathyroid allografts may survive for extended periods, although ultimately they are rejected.] Their second patient received, first, a parathyroid graft from a dog (in the axilla) and a second graft from a human. Her serum calcium level rose from 6.6 to a high of 11.5 mg/dL and all symptoms of hypocalcemia were abolished. Here again, the follow-up period was only several months.

In subsequent investigations, Stone and Kennedy implanted small thin slices of endocrine tissue from an animal of one species into one of another species (heterografts or xenografts), the tissue being contained in a "millipore filter of a pore size small enough to exclude all animal cells" (Fig. 6).[47] The gradual atrophy and disintegration of this tissue they attributed to starvation of the tissue due to ischemia. [However, as noted above, subsequent studies by others confirmed the role of graft rejection factors as well.] A principal discussor was Dunphy who cautioned against assuming that the rejection reaction had been avoided by use of the millipore filter, which excluded the ingress of host cells.

In 1963 Hardy and Langford presented a paper,[20] where at operation for total adrenalectomy for Cushing's disease, four patients had undergone transplantation of segments of slices of one of the excised adrenals to the right thigh, the implant(s) being inserted into the sartorius muscle in the last two patients. Various degrees of "takes" of these autotransplants had been confirmed by subsequent biopsy under local anesthesia. However, by the time of a subsequent report to the SSA in 1984, Hardy et al.[21] were able to document various degrees of long-term graft survival. It sometimes required years before the implants had gained sufficient parasitic blood supply and size to permit complete withdrawal of replacement therapy. However, one patient had so much growth of the implants that Cushing's disease returned and the autograft "adenomas" had to be excised under local anesthesia.

The next endocrine transplantation paper was that of Diethelm et al.[10] Sixty-one patients with chronic renal failure and secondary hyperparathyroidism had undergone total parathyroidectomy and parathyroid autografting, after the general principles previously established. Diethelm et al.[10] achieved ultimate transplant success from the parathyroid implantations into a sternocleidomastoid muscle. Some of their patients required administration of supplemental calcium after operation, but in no instance did profound hypocalcemia occur and no patient developed recurrent hyperparathyroidism.

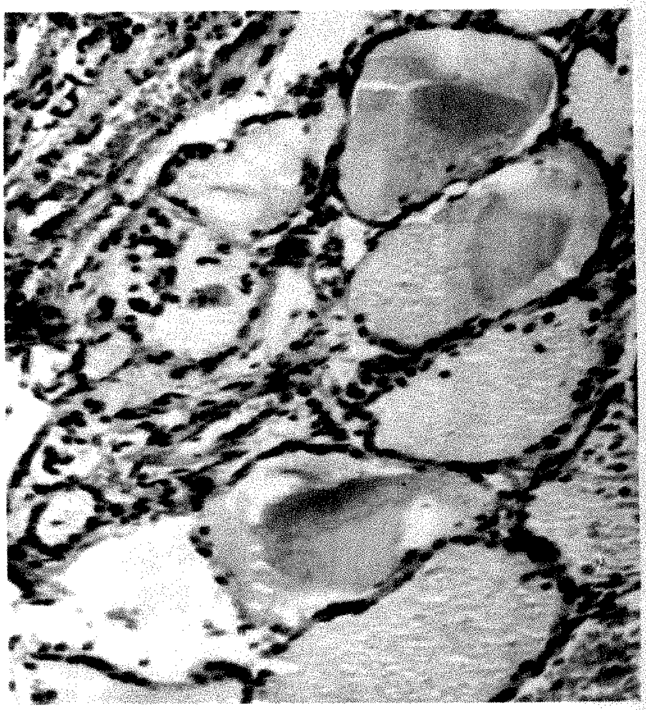


FIG. 6. Living thyroid tissue in heterologous transplant.[47]

The most recent endocrine presentation, at the 1985 meeting, was that of Rossi et al.,[40] who reported eight technically successful transplants of pancreatic segments to the femoral area, with anastomoses to the femoral artery and vein, respectively. Only one of the eight patients required insulin (at 2 years after grafting). They concluded that segmental pancreatic autotransplantation prevents or delays the onset of diabetes mellitus following total or near total pancreatic resection.

Allotransplantation Biology

The publications dealing with transplant operative technique, immunology, and organ preservation have been placed after the orthopedic and endocrine papers because (1) these two did not usually involve vascular anastomoses, and (2) transplantation science truly entered the picture only after homotransplantation (allotransplantation) was begun, usually involving whole organs that had to be preserved while being transplanted and then protected from rejection thereafter. A pivotal presentation was given by Dunphy and Jacob,[14] who emphasized the importance of separating the technical and physiologic problems of autotransplantation, on the one hand, from the additional ones created by introducing the immunologic elements of the rejection reaction, imposed by allografting or heterografting (xenografting). At the 1965 meeting Haller and Jones[18] reported on splenectomy. At that time, some kidney transplanters routinely removed the spleen ("the largest lymph node of the body"). It was already appreciated that lymphocytes (and presumably thymocytes) were key elements in the allograft rejection reaction, and thus any new information relative to splenic immunologic capabilities was potentially applicable to organ transplantation. The authors did find that splenectomy rendered the mammals represented more susceptible to infection, though splenectomy did not significantly extend skin allograft survival in mice so studied.

At the 1970 meeting Wen-Pen Liu et al.[26] detailed that perfusion with Collins' C_5 solution clearly improved organ preservation over the 48-hour period of cold storage prior to allotransplantation into nephrectomized dogs.

Another storage report was that of Starling et al.,[44] who found that methylprednisolone, a lyosomal membrane stabilizing agent, when used to pretreat the donor animal and when added to the kidney perfusate, delayed the onset of vascular resistance changes and diminished lyosomal enzyme concentrations in the perfusate.

Tissue Typing (Matching). The two reports dealing with tissue typing, both germane to the relation of tissue typing to success in renal allotransplantation, were by McDonald et al.[31] and Richie et al.[36] McDonald et al.[31] found that "in general the mixed lymphocyte culture responses parallel differences in HL-A incompatibility and appear to relate to renal allograft survival. . . . The most reliable indication of successful transplantation exists when the donor and recipient are HL-A identical serologically and no stimulation occurs in MLC's between them."[31]

Richie et al.[36] studied the role of HLA typing in cadaveric kidney transplantation. They concluded that their results "supported the concept that better results can be expected when better matched kidneys are utilized for transplantation."[36]

Skin Transplantation

In general, split thickness skin graft reports have not been included in this review of SSA publications, for such transplants had been routine and universally used for so many years. However, the report of Artz et al.,[1] "The Appraisal of Allografts and Xenografts as Biological Dressings for Wound and Burns," was of particular significance because (1) extensive full thickness burns remain so serious a problem, (2) pig skin is more readily obtained than human skin, and (3) of Artz' long and extensive experience in the management of burns. Artz et al.[1] concluded that porcine xenografts were especially useful because they are readily procurable and inexpensive. They were of value in preparation of recipient sites for grafting; in treatment of leg ulcers, decubitus ulcers, and second-degree burns; as cover for mesh grafts; and in protection of large open wounds until autografts are available. Used in the manner they described, porcine xenografts "had shown no immunological properties."[1]

Kidney Transplantation

The renal allograft has been the whole organ prototype on the immunologic basis of which other organs have been transplanted. Thus, it is not surprising that a significant number of important papers dealing with renal transplantation (Fig. 7) have been presented before the SSA. The first clinical report was that of Hardy et al.[22] at the 1966 meeting. Included were one autotransplant for ureteral injury, four cadaver donors, one living sibling donor, and five unrelated living donors.[22] This early report reflected many of the problems that attended clinical kidney allotransplantation at that time, in our university hospital as in many other hospitals throughout the world. The results were less than optimal, but they pretty much represented the general state of the art at that time. We had been obliged to use peritoneal dialysis in lieu of chronic hemodialysis, which was not initially available to us. Infection was a major problem in our patients. The paper was discussed by A. M. Lansing, who reported similar but somewhat better early results with 12 patients. He asserted that the successfully transplanted patient had a much superior quality of life than did the patient on chronic dialysis—a conclusion that was much disputed by nephrologists in those early days of clinical renal allotransplantation. Other informative presentations included work by Flanigan et al.[16] and McDonald et al.[29]

Deithelm et al.[12] reported at the 1975 meeting a retrospective analysis of 100 consecutive patients undergoing related living donor renal transplantation. Rehabilitation was good in 76% of the living patients and poor in only 4%. These same workers, in a related study presented in 1979, reviewed impaired renal function.[11]

Another carefully considered and prepared report (1979) was that of Pfaff et al.[35] HLA identical grafts showed the expected advantage compared with single haplotype grafts (93 *vs.* 74%).[35] Rohr[38] found the morphology abnormal in the post-transplant biopsy (taken at operation) in all 22 kidneys that had exhibited delayed graft function. However, four kidneys that had structural abnormalities in the procurement biopsies had functioned normally. A total of 57 cadaver allotransplants had been studied.[38]

Fish[15] utilized the technique of lymphocyte depletion

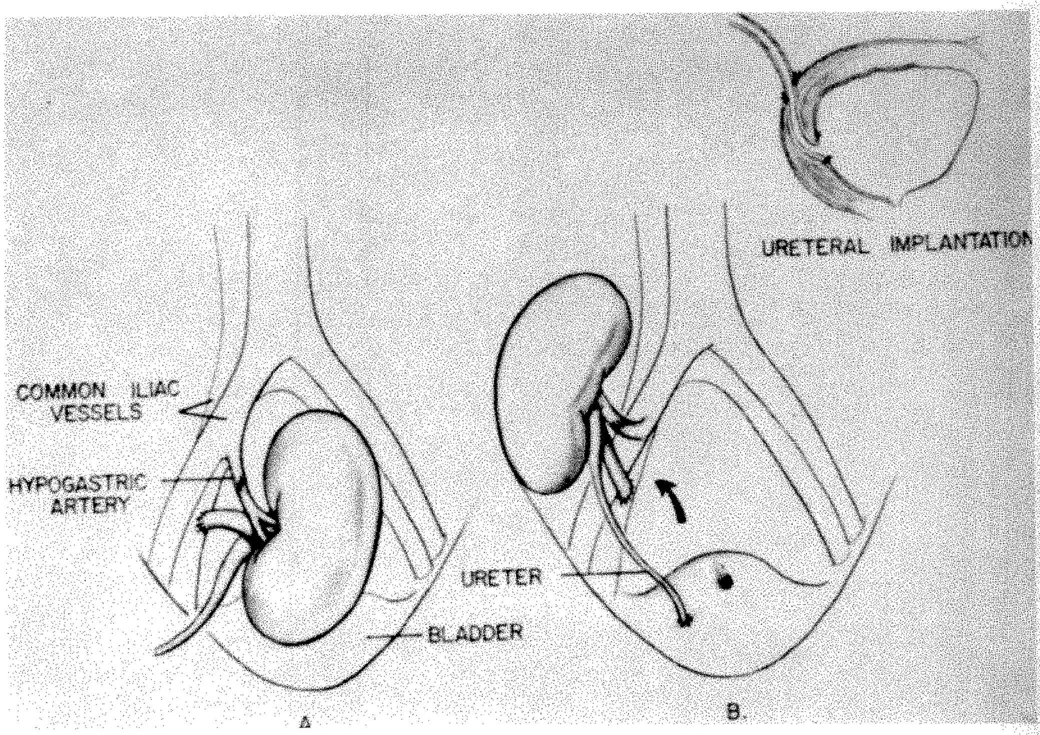


FIG. 7. Technique of kidney transplantation.[22]

by thoracic duct drainage as a method of immunosuppression in clinical kidney allotransplantation.

Richie et al.[37] studied 389 transplants performed from June 1977 to December 1981. Two-hundred fifty-three patients received cadaver kidneys and 136 patients obtained kidneys from a relative. Many factors were considered additive in permitting successful kidney allotransplantation.[37]

Biliary–Alimentary Tract Transplantation

Only two publications involved the biliary–alimentary tract. In Myers et al.[32] homografts of common bile duct and free autogenous grafts of vein, artery, and common bile duct to repair defects in the common bile duct of the dog failed in these experiments. In fact, up until now no substitute for the common bile duct has been developed, though bypasses using various elements of the stomach, duodenum, or, especially, the jejunum have served reasonably well. As yet there have been no liver transplantation publications in the Transactions.

Jejunum was transplanted clinically (Fig. 8), as reported by McDonald et al.[30] Their work extended still further the pioneer basis of the clinical autotransplantation of the organs involved, that is, kidney, jejunum, and pancreas.

Lung Transplantation

The only report dealing with lung transplantation *per se* (Fig. 9) was that of Hardy et al.[19] Studies had been performed in 215 dogs: survival on a single reimplanted lung, respiratory physiology of transplanted lungs, regeneration of lymphatics and pulmonary innervation, lung storage prior to transplantation, lung allotransplantation using a variety of immunosuppressive modalities, and presentation of a clinical case in whom lung transplantation could possibly have been life-saving and morally acceptable.[19] [The first human lung transplantation was to be performed 6 months later.]

Vascular Transplantation

The intense worldwide interest in peripheral vascular surgery, which burgeoned after the experience gained with direct repair of such injuries in the Korean War, was reflected in a number of reports before the SSA dealing with transplants as arterial substitutes. The feasibility of venous autotransplants and of arterial autografts and allografts was fully established experimentally by Carrel and Guthrie at the turn of the century, and first used clinically by Gross who in 1948 reported the successful use of aortic homografts to correct coarctation of the aorta where the involved segment was too long to permit its resection and primary end-to-end anastomosis. Fabric substitutes were under intensive study, but there was also investigation of a variety of biologic substitutes as well.

At the 1968 meeting Dale and Lewis[8] reported the use of modified bovine heterografts for arterial replacement;

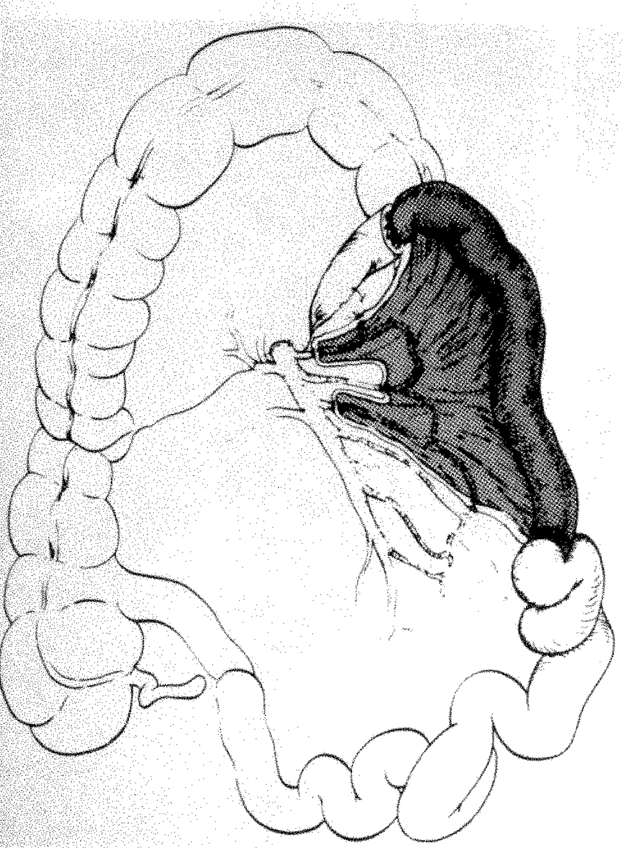


FIG. 8. Technique for excision of a segment of small intestine for transplantation.[30]

carotid arteries were removed under sterile conditions in the slaughterhouse, placed in iced water, and then treated with specified processing in the investigators' laboratory. In their review of the literature, the authors had noted that experimental and clinical results with heterografts had been attended by a high failure rate due to thrombosis, rupture, and aneurysm formation. However, their modified bovine heterograft had been used as femoral or popliteal replacement in 12 patients with favorable preliminary results. Follow-up study to 35 months had shown no aneurysm formation, and patency continued in seven of the 12 grafts placed.[8] N. Kouchoukas and J. R. Jude both discussed use of the porcine heterograft for aortic valve replacement. D. Rosenberg reported his group's use of the bovine vascular heterograft for arterial reconstruction in over 40 patients. Their results thus far were satisfactory.

Ochsner et al.[33] reported in 1970 their experience with fresh venous allografts as an arterial substitute; they had used 22 such fresh venous allografts in 22 patients. Eleven of the 22 were later shown to be occluded. The authors suggested that compatible matching within the ABO system might enhance allograft success.[33]

Microvascular Transplantation

One of the most remarkable examples of progress in transplantation has been the ever more sophisticated anastomosis of smaller and smaller blood vessels, permitting successful autotransplantation of various body tissues with immediate reestablishment of blood flow through the tissue at its new site. This has permitted repair of major body surface and deeper tissue defects.

Serafin and Georgiade[41] presented a study on microsurgical composite tissue transplantation. Since 1974, 69 patients with extensive defects had undergone reconstruction by microsurgical composite tissue transplantation. In the series, transplantation in 56 patients (81%) had been completely successful. They emphasized that healthy, well vascularized tissue could now be transferred to a distant previously irradiated area with no tissue loss.

At the 1981 meeting Jurkiewicz and Nahai[24] presented a report on the use of the omentum as a free vascularized graft for head and neck reconstruction (Fig. 10). The omentum had been so used in 18 patients, with most gratifying success.

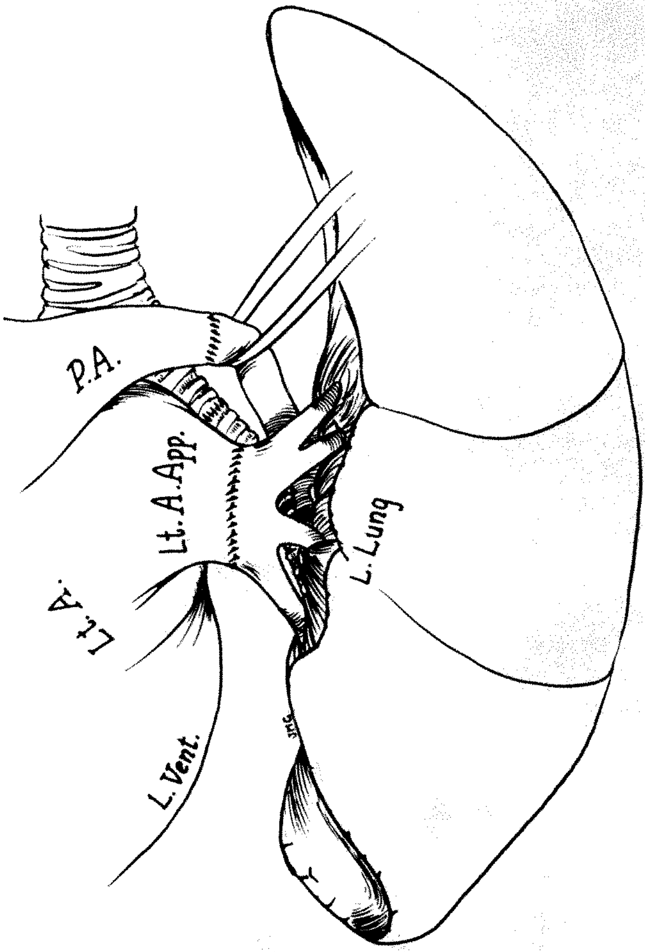


FIG. 9. Technique of lung transplantation.[19]

Transplantation Involving the Heart

The modalities of tissue transplantation involving the heart were vein autotransplants in coronary artery bypass, valve replacement with homografts (allografts) or porcine heterografts (xenografts), and total heart transplantation.

At the 1968 meeting Karp and Kirklin[25] reported on replacement of diseased aortic valves with homografts; their group was a world leader, with this extensive and successful experience with 70 aortic valve homografts.[25]

At the 1970 meeting Spencer et al.[42] reported on bypass grafting for occlusive disease of the coronary arteries. At that time this was a very substantial experience with an operation not yet fully accepted for relief of myocardial ischemia. Autografts of the saphenous vein were combined with use of the internal mammary arteries (Fig. 11). The mortality rate was 10%, and the overall success achieved was impressive.[42] Another important report by Spencer et al.[43] involved extensive data supporting their conclusions that "excellent results with porcine prostheses in the first 4–5 years" could be achieved.[43]

The first SSA report involving heart transplantation was that of Denton A. Cooley et al.[6] They had performed heart transplantation in 17 patients (Fig. 12). Their results were, at this very early stage of heart transplantation, spectacular, though most of the serious posttransplant problems germane to this field of activity at that time had been chronicled.[6] Early deaths were due to "acute cardiac rejection after one week, and one each from preexisting diseases and complications of immunosuppressive therapy, respectively."[6] Two deaths later occurred from sepsis. Three patients died at from 5 to nearly 7 months after operation from chronic cardiac rejection. [Barnard had performed the first successful clinical heart transplantation in 1967.] The paper was discussed by Hardy, who showed a motion picture of the first heart transplantation (chimpanzee) in man in 1964. W. R. Webb discussed the physiologic and immunologic considerations of heart transplantation on the basis of his long and extensive experience with experimental heart transplantation.

At the 1986 meeting Gray et al.[17] presented a report of a successful cardiac transplantation program using combined university and community resources.

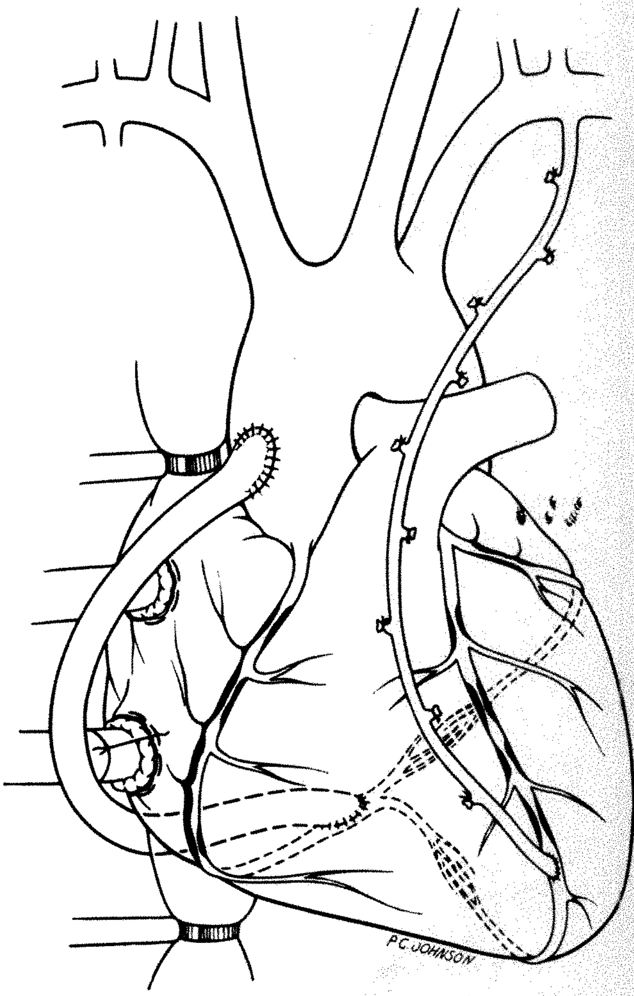


FIG. 11. Technique of saphenous vein autotransplantation for coronary artery bypass.[42]

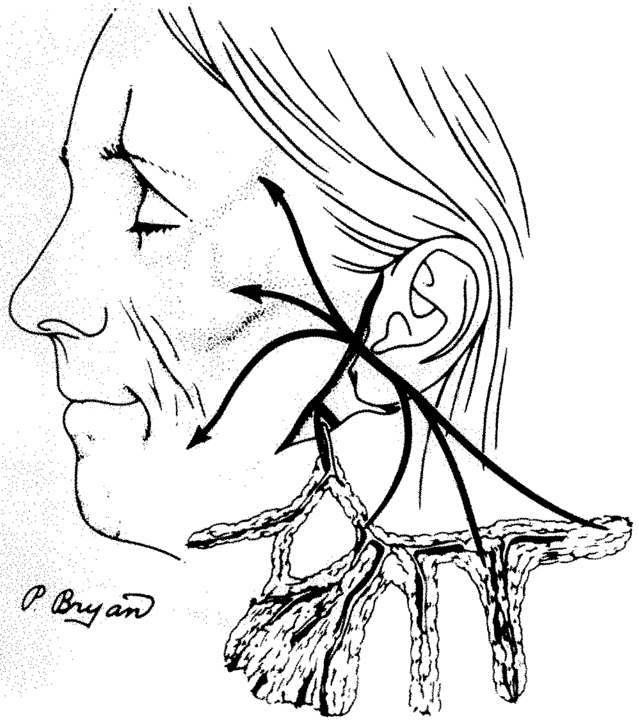


FIG. 10. Technique of omental autotransplantation for repair of facial defects.[24]

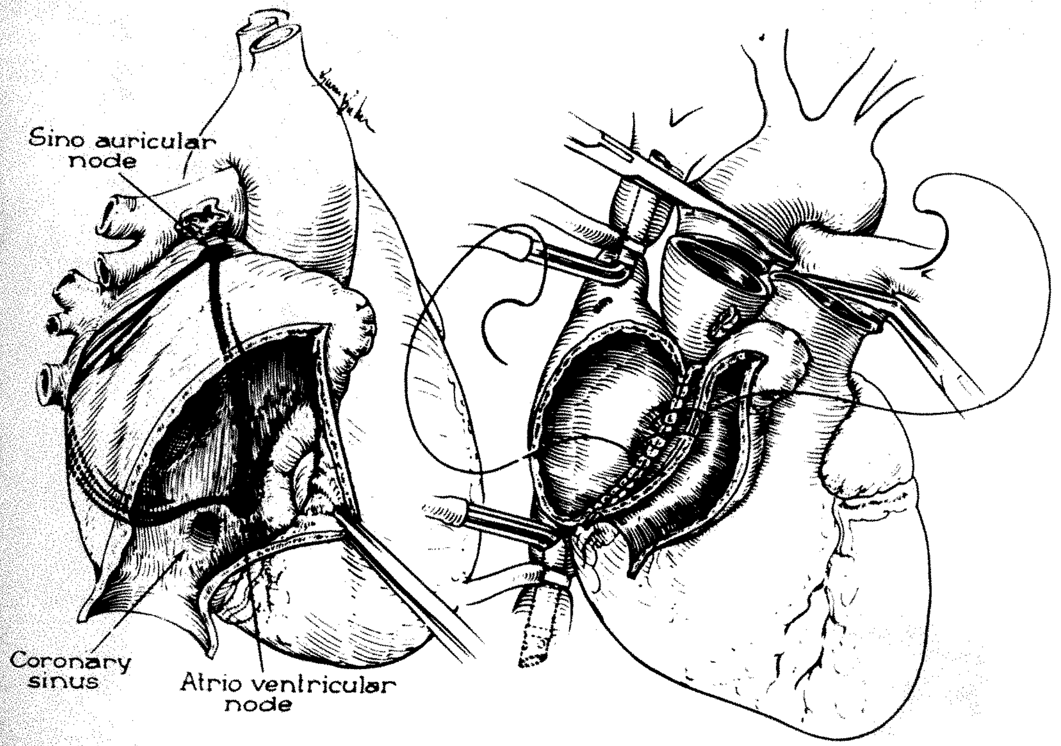


FIG. 12. Technique of heart transplantation.[6]

The Multiple Organ Transplant Program

The final paper in this review of transplantation of organs and tissues presentations before the SSA highlights the climax of cumulative experience with clinical organ transplantation during the SSA's first century. At the 1985 meeting Bahnson et al.[2] presented their experience with the development and organization of a multiple organ transplantation program. They had established in Pittsburgh possibly the foremost multiple organ transplant center in the world.

Conclusions

We now stand poised to achieve routinely successful clinical transplantation of most organs. And it has been well said that organ transplantation is the general surgeon's tomorrow. Who can doubt its vast influence on clinical surgery during the Southern Surgical Association's second century?

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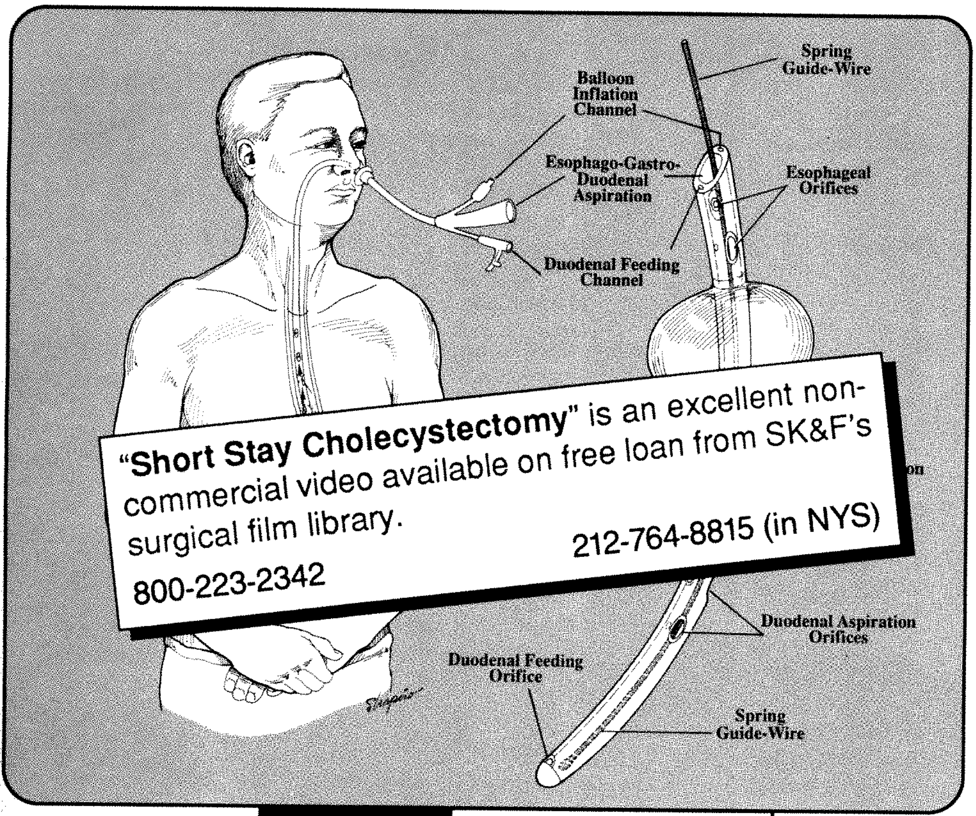

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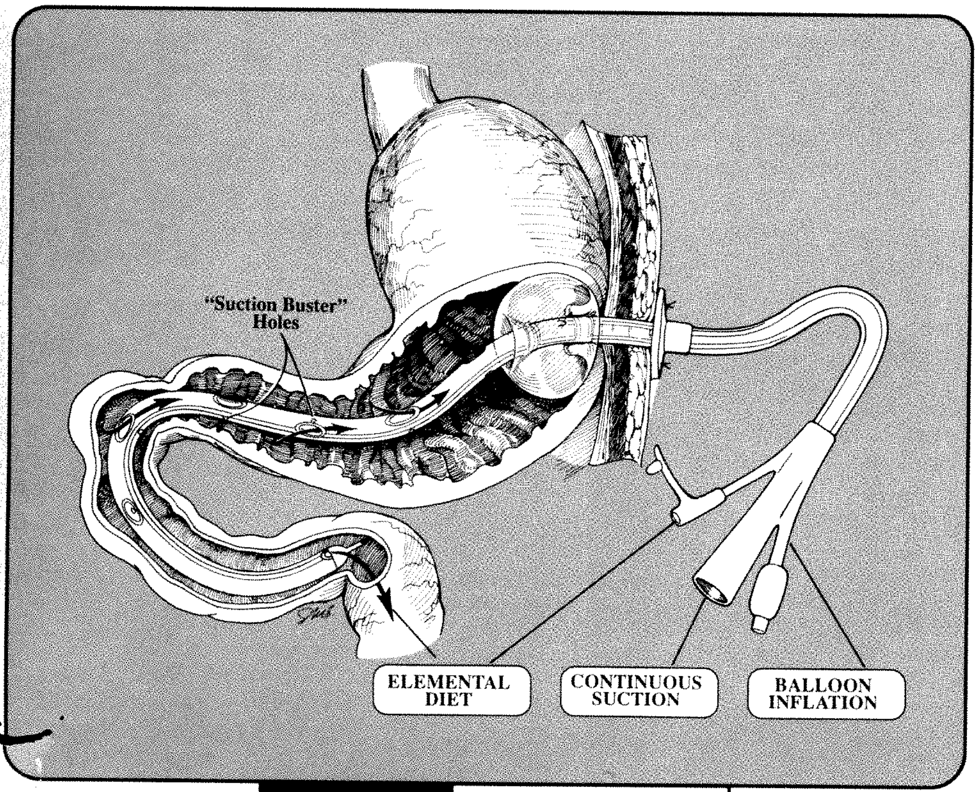

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CASE # 24 **AGE:** 55 **SEX:** FEMALE

DIAGNOSIS: CECAL CARCINOMA

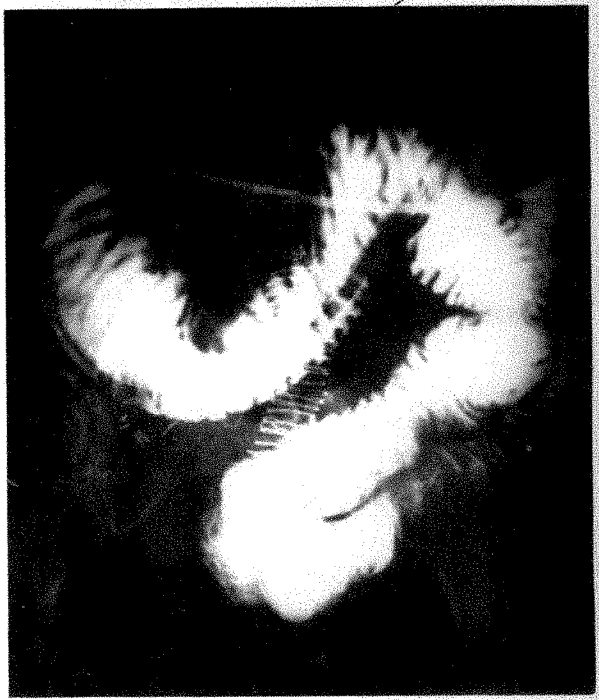
SYMPTOMS: ANEMIA (Hg 6 gm/dl)

OPERATION: RIGHT HEMICOLECTOMY & GASTROSTOMY

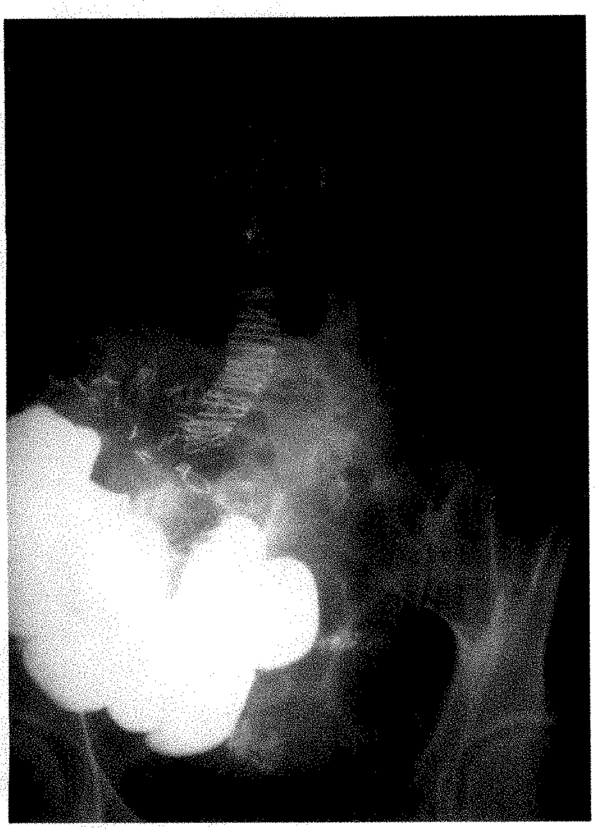
The patient had a right hemicolectomy with stapled (U.S. Surgical Corp) anastomosis and fascia closure and a MOSS® gastrostomy tube. The stomach and proximal duodenum were aspirated, with immediate simultaneous feeding into the distal duodenum.

Barium feeding 5 hours postop documented adequate motility. The deliberate excess was totally removed. No contrast (i.e.: excess feeding) escaped efficient aspiration within the proximal duodenum, to reflux into the stomach. (Figure A) Serial motility study showed barium had traversed the anastomosis and colon, and already was exiting in a spontaneous bowel movement by 21 hours postop. (Figure C)

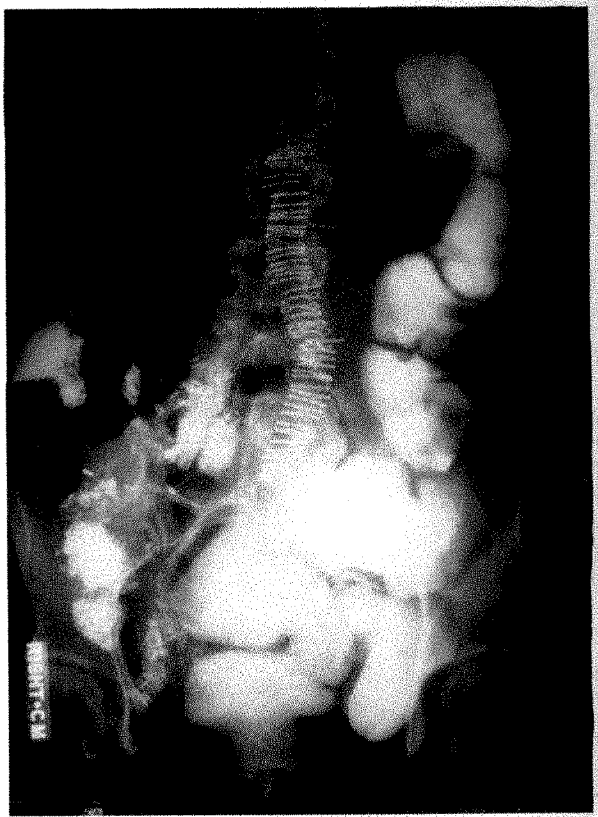
She received 300 ml/hr of Vivonex TEN (Norwich Eaton Pharm), absorbed 5,000 kcal the initial 20 hours, and then tolerated a general diet. She was the 4th patient discharged uneventfully 24 hours after bowel resection and reanastomosis.



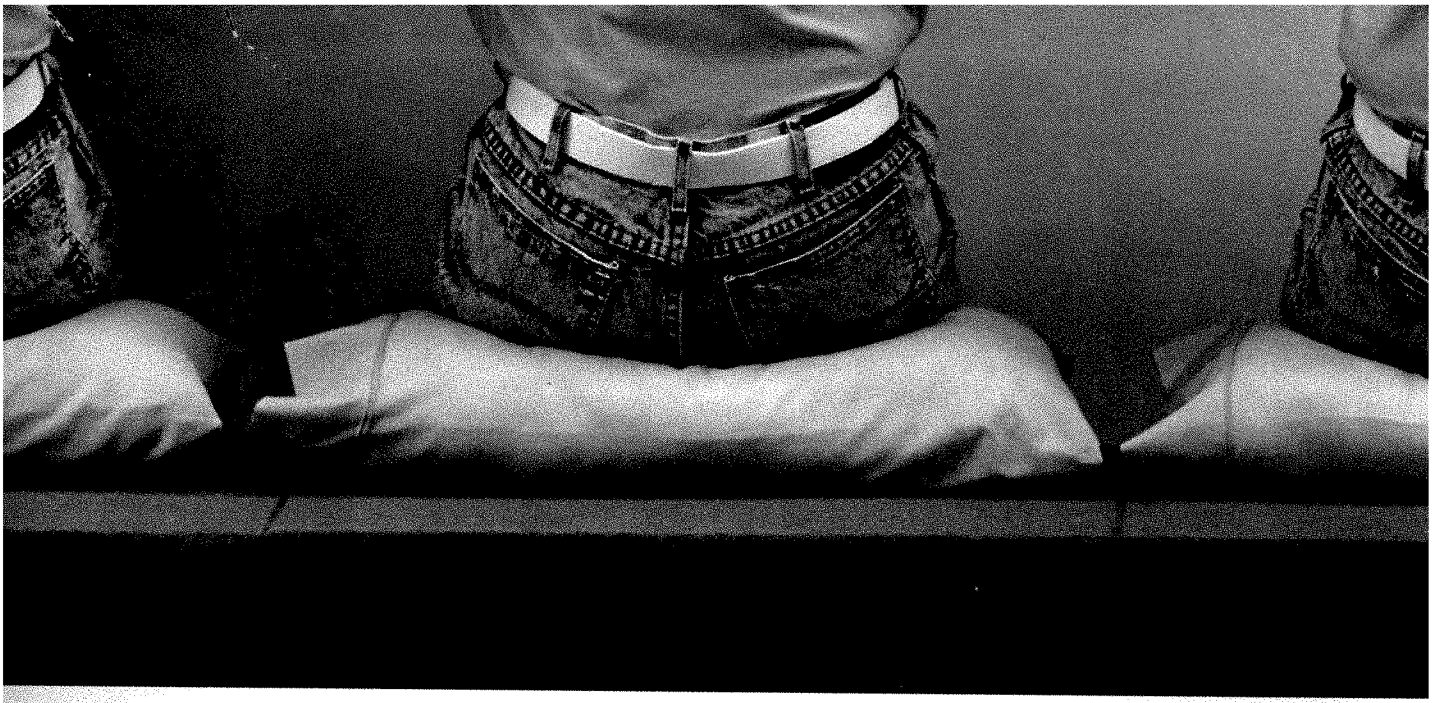
A. Study @ 5 minutes (5 hours postop).
Note efficient removal of all excess barium, with none reaching the stomach.



B. Motility @ 4 hours (9 hours postop).
All barium is within the ileum.



C. Motility @ 16 hours (21 hours postop).
Barium is exiting in a spontaneous bowel movement.



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INDICATIONS AND USAGE: Topical corticosteroids are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.
CONTRAINDICATIONS: Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.
PRECAUTIONS: ***General:*** Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia and glucosuria in some patients. Conditions which augment systemic absorption include the applications of the more potent steroids, use over large surface areas, prolonged use and the addition of occlusive dressings. Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area and under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids. Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See PRECAUTIONS—Pediatric Use.) If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted. In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.
Information for the Patient: Patients using topical corticosteroids should receive the following information and instructions: 1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes. 2. Patients should be advised not to use this medication for any disorder other than for which it has been prescribed. 3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician. 4. Patients should report any signs of local adverse reactions especially under occlusive dressing. 5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.
Laboratory Test: The following test may be helpful in evaluating the HPA axis suppression: ACTH stimulation test
Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids. Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.
Pregnancy Category C: Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women of teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.
Nursing Mothers: It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities NOT likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when any topical corticosteroids are administered to a nursing woman.
Pediatric Use: Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio. Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches and bilateral papilledema. Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.
ADVERSE REACTIONS: The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximately decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, miliaria.
OVERDOSAGE: Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects. (See PRECAUTIONS.)
DOSAGE AND ADMINISTRATION: Topical corticosteroids are generally applied to the affected area as a thin film three or four times daily depending on the severity of the condition. Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions. If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted.
HOW SUPPLIED: 1 oz. tube with rectal applicator.
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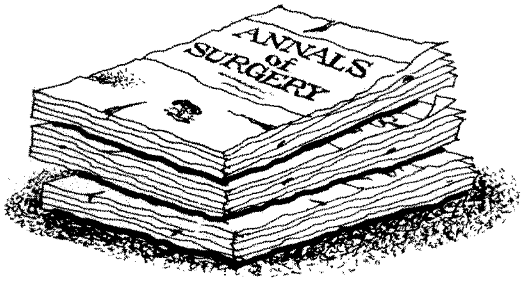

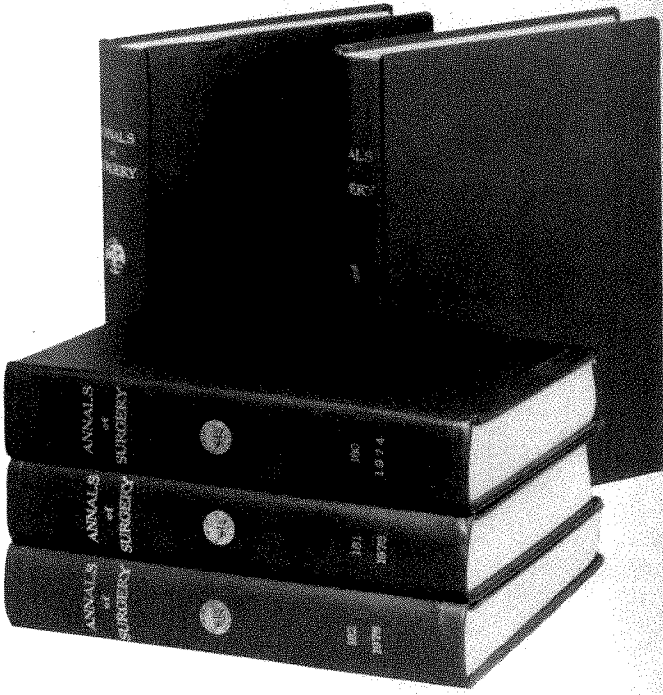

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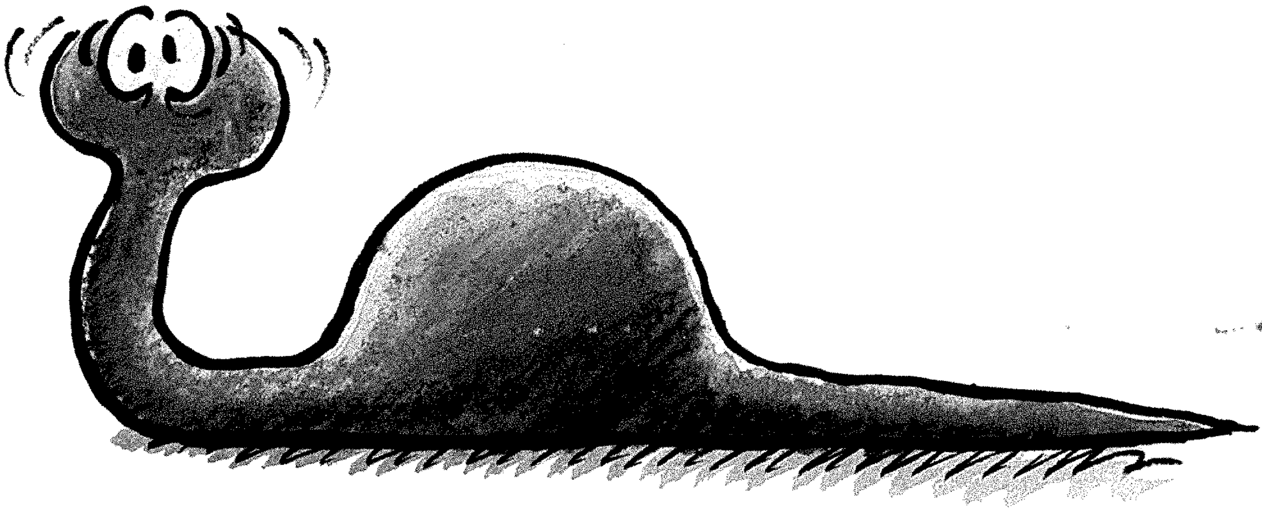

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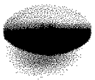

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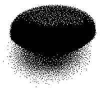

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